Appendix 6 Cost effectiveness analysis for Barrett's oesophagus

1 Introduction

The National Institute for Health and Clinical Excellence (NICE) has been asked to produce a guideline on the use of ablative therapies for the treatment of people with Barrett's oesophagus. This is the cost effectiveness analysis developed to support the guideline development group (GDG) in making recommendations. The analysis was conducted according to NICE methods outlined in the Guide to the methods of technology appraisals, 2008 and the Guidelines Manual 2009. Therefore, it follows the NICE reference case (the framework NICE requests all cost effectiveness analysis to follow) in the methodology utilised.

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3 Decision problem

Table 1 outlines the decision problem that will be addressed in this guideline and based on the final scope

Table 1 Decision problem

	Scope	Approach taken
Population	People with high grade dysplasia (HGD) and intramucosal cancer	People with HGD from 60 till death
Interventions	Endoscopic therapies	Endoscopic mucosal resection (EMR), radiofrequency ablation (RFA), photodynamic therapy (PDT), argon plasma coagulation (APC), and any combination of EMR with ablation
Comparators	Surveillance, surgery	No surveillance, surveillance and surgery
Outcome(s)	Costs, QALYs and Cost per QALY	Cost per QALY

3.1 Population

The choice of 60 as the age of the cohort was based on advice from the GDG that in the UK the majority of Barrett's is diagnosed at 60 years. It will be assumed that high grade dysplasia (HGD) and intramucosal cancer are the same and therefore will not be split. This assumption is reasonable since clinicians treat these conditions in the same way. A limitation is that there is likely to be different rates of cancer progression between them. This could subsequently lead to an underestimation of the potential benefits of surveillance.

3.2 Interventions

From the clinical review MPEC and laser do not have enough evidence to justify their use and therefore shall not be considered. EMR, RFA, PDT, APC and any combination shall therefore be considered.

Currently there is no guidance on whether these treatments should be given alongside a surveillance programme. It is unlikely that in clinical practice that these therapies could be ethically given without some form of post treatment surveillance to monitor the condition. Therefore, for the base-case these therapies will be considered with surveillance and then analysis will be conducted to explore its effect.

3.3 Comparators

Current information from the British Society of Gastroenterologists guidelines (Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus 2005.) and British Thoracic Surgeons Guidelines (Fernando et al 2009) recommend that people with Barrett's oesophagus with HGD should be included in a surveillance programme and potentially preventative surgery as an option. Surgery in this case is assumed to be a full oesophagectomy. However, surveillance is not consistently offered across the NHS and therefore, all three will be considered as potential comparators. There is the possibility that surgery is an inappropriate comparator since not all those eligible for endoscopic therapy will be eligible for surgery. This will be explored in the discussion section.

The surveillance programme implemented in the model is based on BTS guidelines. Table 2 outlines the surveillance schedules that will be implemented in the model based on existing guidelines and GDG opinion.

Table 2 Surveillance schedule

State	Schedule
No Barrett's oesophagus	None
Non dysplastic Barrett's oesophagus	Every two years
Low grade dysplasia	Every six months
High grade dysplasia	Every three months

These will not be varied since this guideline will not produce recommendations on the use/effectiveness of surveillance. However, for

people with active treatment the GDG advised that the strategy used is different and is outlined in table 3.

Table 3 Active treatment surveillance strategy

State	Schedule year 1	Year 2	Years 3-5	Thereafter
No Barrett's oesophagus	Every 3 months			
Non dysplastic Barrett's oesophagus	Every 3 months	Every 6 months		
Low grade dysplasia	Every 3 months	Every 6 months	Every year	Every two years
High grade dysplasia	Every 3 months	Every 6 months	Every year	Every five years

3.4 Outcomes

In line with the NICE reference case a cost utility analysis will be used to analyse the cost effectiveness of ablation techniques.

4 Review of existing cost effectiveness analyses

4.1 Search for cost effectiveness analyses

A search for cost effectiveness, quality of life and resource papers was carried out (see appendix 3). These papers were then subject to a systematic search. Papers were initially excluded on the basis of the title, subject, intervention, condition etc. Of the remaining papers abstracts were then searched to see if they contained relevant data. The remaining papers were then categorised into: cost effectiveness – ablation, cost effectiveness – natural history, quality of life and resource use. These papers will be reviewed in the following sections.

4.2 Review of cost effectiveness studies – Ablation

After the initial search 8 studies were identified that examined ablation therapy in patients with high grade dysplasia. These were reviewed with checklists to assess their applicability to the decision problem and limitations in regard to their methodology. These are produced in section 13.3 and 13.4. A GRADE table which summarises the studies is presented in section 13.5.

A study by Gerson et al 2004 was excluded even though it included EMR and PDT because it was only for the treatment of cancer and not HGD. In addition, it did not include utilities or a comparison between EMR and PDT.

After review none of the studies were considered of high quality or applicable to the decision problem and all have limitations. Therefore, a de novo model will be required to address this question. These papers do provide valuable information on the potential methodologies and therefore will not be excluded from consideration.

4.3 Potential modelling approach

Barrett's oesophagus is a lifetime chronic condition; therefore, the model will incorporate a lifetime horizon is required. A Markov model or discrete event simulation (DES) would appear to be most appropriate. A DES in this case seems inappropriate since the data available does not allow us to fully utilise all its features, and therefore a Markov model will be constructed. The states will represent the progression of the condition over time from no Barrett's oesophagus (NBO), non-dysplastic Barrett's oesophagus (BO), low grade dysplasia (LGD), high grade dysplasia (HGD), asymptomatic cancer (also referred to as early cancer) and symptomatic cancer (also referred to as late cancer). In many of the cost effectiveness studies identified a decision tree was used to model treatment and then a Markov model was used for the disease progression. This would be possible but re-treatment is a possibility, potentially many years into the future. To do this within a decision tree/Markov model would be time consuming and overly complicated, possibly resulting in miscalculations. Therefore, Markov nodes will be included that simulate the treatment process. This requires an assumption over the cycle length to ensure that patients do not spend too long in a treatment state. It was considered that a cycle length of a month would be most appropriate as it is small enough for transitions between surveillance visits.

A major component of other models in this area is the inclusion of diagnostic states to replicate the unmonitored progression of the condition and the possibility that a patient diagnosed as LGD may progress to cancer before

their next surveillance visit. The model will therefore include diagnostic states for NBO, BO, LGD and HGD.

Another issue is that once cancer is diagnosed surgery is currently standard care. However, chemoprevention is growing in popularity. Since there is no current data on this procedure it will not be included, also surgery is still recommended in most guidelines. In all the models considered once surgery is performed all patients enter a post-surgical state. In this state they can only die of natural causes or develop cancer. This is a simplifying assumption that was put to the GDG since post surgical data is not extensive. The GDG concluded that this was an acceptable assumption to make.

4.4 Natural history review

A major component of Barrett's oesophagus models is the inclusion of natural history. This component allows the clinical results of treatment to be extrapolated to a life time horizon to account for the long term benefits and costs of treatment. Due to time and resource constraints a full systematic review of natural history data to calculate transition probabilities was not possible. Therefore, all cost effectiveness studies were reviewed to provide estimates for the progression of Barrett's oesophagus. A total of 18 studies were identified that examined only surveillance plus the 8 identified studies for ablative therapy for Barrett's oesophagus.

These studies were examined for suitable transition probabilities for a Markov model which resulted in 4 being rejected. 14 of the remaining studies contained transition probabilities suitable for inclusion in an economic model. The papers with appropriate transition probabilities are reported in table 4.

Table 4 Transition probabilities from ablation/surveillance studies

From	To	Chin Hur 2003	Inadomi 2003 & Rubenstein 2007	Sonnenberg 2003 & 2002	Nietert 2003	Chin Hur 2004	Shaheen 2004	Vij 2004	Garside et al 2006	Gerson 2004 &2007	Das et al 2009	Inodomi et al 2009*
No Barretts oesophagus	Non dysplastic Barrett's		0.005									
Non dysplastic Barrett's	LGD		0.05		0.045	0.065	0.05	0.005	0.0289	0.04	0.05	0.0275
Non dysplastic Barrett's	HGD		0.01		0.01		0.01			0.015	0.01	0.0055
Non dysplastic Barrett's	Cancer		0.005	0.005		0.005	0.005			0.005	0.005	0.0028
LGD	HGD		0.05		0.095	0.165	0.05	0.007	0.0345	0.05	0.05	0.0275
LGD	Cancer		0.025				0.025	0.005		0.04	0.01	0.0138
HGD	Cancer	0.15-0.10	0.055	0.05		0.155	0.025	0.074	0.1187	0.05	0.07	0.0303
Cancer	Dead					0.28		0.4	0.78			
early cancer	late cancer							0.14	0.143			
Non dysplastic Barrett's	norm		0.0175				0.0175		0.0243		0.0175	
LGD	BO		0.63			0.348	0.63	0.002	0.1291	0.3		0.3465
HGD	BO		0.1				0.1			0.1	0.1	0.0055
HGD	LGD		0.07			0.148	0.07	0.163	0.0476	0.1	0.07	0.0385

Sonnenberg 2002 and Sonnenberg 2003 are based on the same model and therefore, the 2002 paper will be considered alone. Rubenstein 2007 is based on Inadomi et al 2003 so only Inadomi et al 2003 will be considered. Gerson et al 2007a is based on an earlier model from 2004 with the same natural history estimates; only the 2004 model will be considered as this includes details of the sources of evidence. This leaves seven studies for consideration. A full review is unnecessary since only the derivation of the transition probabilities and how they were derived is of interest. NICE methods (Guide to the methods of technology appraisals 2008) recommend that parameters should be chosen in a systematic way and based ideally on a systematic review. Table 5 identifies the source of the values in each of the seven studies

Table 5 Source of clinical data in ablation/surveillance studies

Study	Systematic search	Systematic review
Garside et al 2006	Yes	Yes
Inadomi et al 2003	Yes	No
Chin Hur 2004	No	No
Nietert et al 2003	No	No
Sonnenberg 2002	No	No
Gerson et al 2004	Yes	No
Inadomi et al 2009	Yes	No

The conclusion of this quick review is that Garside et al 2006 was the most robust source of transitions. The other papers are compromised by lack of a systematic approach to the selection of values. A full review of Garside et al 2006 is presented in section 13.6. This review concludes that the paper is of high methodological quality and follows the guidelines outlined in the NICE reference case. It will therefore be the main source of data on natural history.

From the reported values the rate of cancer development from HGD appears to have varied the most. It is also likely to be an important variable as it the primary event ablation is expected to prevent. Values varied from 0.03 (Inadomi) to 0.15 (Chin Hur). A systematic review (Wani et al 2009) was identified that analysed the rates of cancer development in Barrett's

oesophagus. This paper followed the guidelines of a good systematic review and appears a robust estimate for cancer progression. This paper concluded, and the GDG agreed, that an annual rate of progression was approximately 7% from high grade dysplasia to cancer.

Garside et al 2006 assumes that the development of Barrett's oesophagus is a stepwise progression. The GDG stated that the natural history for Barrett's oesophagus was not a gradual development, but rather that sudden progressions were possible as described by the probabilities noted in Inadomi et al 2009 and Gerson et al 2007a. However, these estimates are not robust so a Bayesian approach will be utilised to enable unobserved transitions. Further details are provided in the transition probability section (section 5.2).

5 Model

5.1 Model structure

Figure 1 shows the basic outline of the model with the main features highlighted. The main components are the treatment strategy, natural history, post surgery and surveillance.

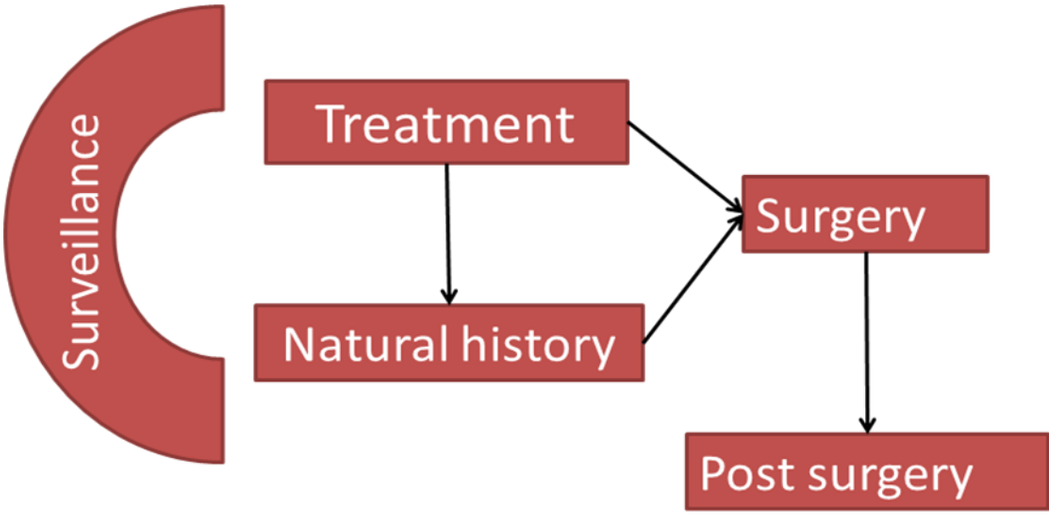

Figure 1 Outline of cost utility model

Each section will now be discussed in detail.

5.1.1 Treatment

In the treatment pathway a Markov state is used to represent the treatment the patient receives, such as EMR, ablation or surgery. It is also assumed that this state is associated with one cycle of time; however, patients can receive a cost and potentially a utility decrement from receiving treatment. The state includes the treatment and observations to ascertain the degree of response. There is also the possibility of more than one treatment being given. For example on average 1.8 EMRs were undertaken (from Ell 2007). This will therefore be used in the calculation of the costs and potentially the HRQoL

The outcomes from this state are determined by the clinical trials of the ablation therapies. The main outcomes are the proportion of patients achieving a complete ablation of Barrett's (NBO), complete ablation of dysplasia (non-dysplastic Barrett's oesophagus, BO), partial ablation of dysplasia (LGD) and no response (HGD). In addition, other outcomes can include perforation (PER) of the oesophagus which would result in surgery in the next cycle. As a base case assumption patients who didn't respond went into surveillance.

Preventative surgery for HGD is modelled similarly as the treatment for cancer.

5.1.2 Surveillance/natural history

Surveillance and natural history follow a similar structure to that described in the Garside et al 2006. A full diagram is presented below figure 2.

The main difference is that there is a separate diagnostic state for no Barrett's oesophagus. This is required to account for those who achieve complete ablation of Barrett's oesophagus. Surveillance is assumed to be undertaken as an endoscopy at the beginning of the cycle patients are then re-allocated to the appropriate diagnostic state at the same time. Patients then progress and regress as normal in the new states. Patients who develop symptomatic cancer (Cans) go on to receive surgery as treatment. Asymptomatic cancer (cana) is only detected via endoscopy, where early surgery can be performed.

If someone who had treatments and achieved a complete or partial response previously (NBO, BO and LGD) can go on to receive another round of treatment. Those who have surgery (oesophagectomy) will go into post surgery states. It is important to note that the treatments do not affect the underlying treatment progression. The effect of treatment is to remove dysplasia (NBO or BO) and then treatment has no further effect on the progression of Barrett's.

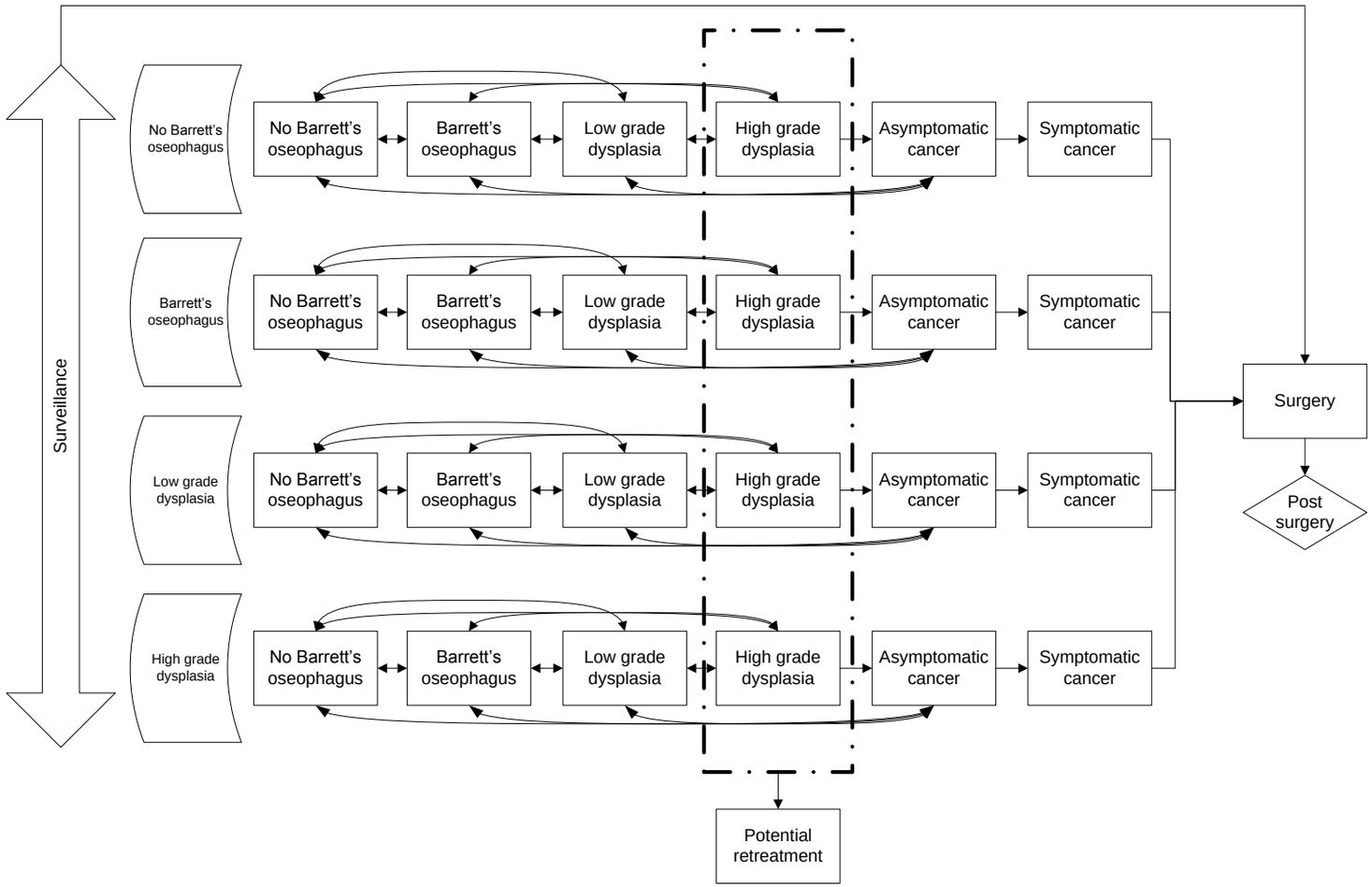

Figure 2 Schematic of natural history

5.1.3 Cancer

The diagnosis of cancer results in the patient being considered for surgery with curative intent. This will include patients receiving chemotherapy and radiotherapy; however, this will only affect the costs and not the utilities.

5.1.4 Adverse events

The model uses two methods for accounting for adverse events. The adverse events that were considered were perforations and strictures. For perforations since the treatment is surgery any health related quality of life loss will be accounted for by the surgery. For strictures a proportion will be calculated from the number receiving the treatment and take into account the health related quality of life impact and cost. But there will be no separate state since this is assumed to not affect the treatment pathway.

5.1.5 Post surgery states

The simplified post surgery states are presented in figure 3. The health states in this model represent complications from surgery, cancer that cannot be treated with surgery and post surgery well.

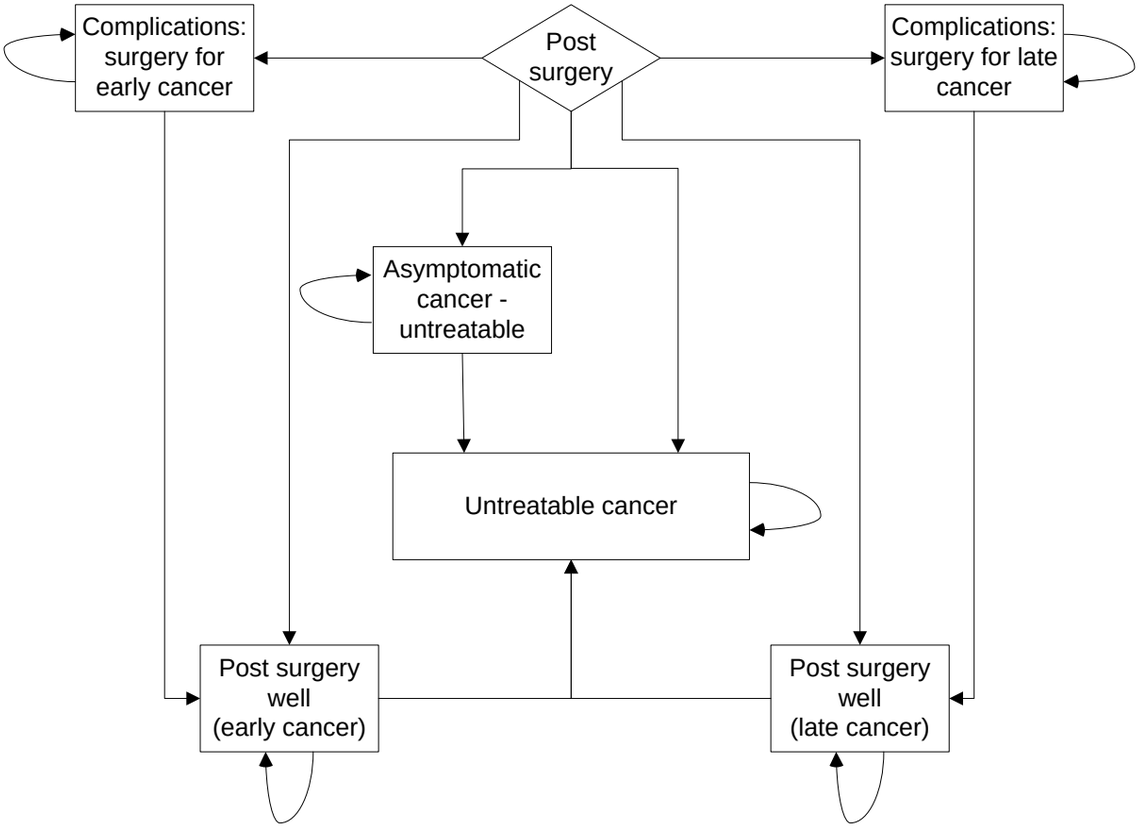

Figure 3 Schematic of post surgery model

The main consideration is that in this model the long term outcomes from surgery depend on when the cancer was detected. This affects the proportion that can be treated with surgery and the long term probability of recurrence of cancer. Therefore, the structure is designed to distinguish between those who have had surgery for a cancer detected when it is still asymptomatic and those when the cancer is only detected due to symptoms. Therefore, for those whose cancer is detected asymptomatically those considered unsuitable for treatment will transit to the asymptomatic cancer state. Those who have surgery can die from the surgery, suffer complications or go straight to a post surgical well state (early). The same holds for those detected symptomatically except that those considered unsuitable for treatment transit straight to untreatable cancer. People can transit to death from all states. Those in the post surgical well states who have a recurrence of cancer transit to the untreatable cancer state.

For those who have surgery for HGD everything remains the same except that the rate of recurrence of cancer is changed since the oesophagus was removed before cancer developed.

This is a simplified version of post cancer treatment and subsequently there is no additional therapy and therefore could underestimate the post surgery survival. However, oesophageal cancer is associated with very poor outcomes. In addition, SIGN guidance and BSG guidance suggests that there are few options post surgery for the treatment of cancer.

5.2 Transition probabilities

There are three sets of transitions included in the model, natural history, post surgery and treatment related. The details of the chosen values are outlined in the following sections. Below are details of how these were incorporated into the model.

5.2.1 Natural history

The probabilities derived from Garside et al 2006 were chosen as the most robust as they were based on a full systematic review. Mortality from NBO, BO, LGD, HGD and asymptomatic cancer are assumed to be age dependant. Data from published interim life tables for the UK (Office of National Statistics, 2009) was used to produce age related mortality probabilities. It was unclear from Garside et al 2006 whether there was a separate transition estimate from the cancer states due to higher mortality from cancer. It shall be assumed that patients in the asymptomatic cancer states have a probability of dying the same as the age related probability. This appears to be reasonable since asymptomatic patients are unlikely to have an increased risk of death until their cancer progresses. For symptomatic the estimate for untreatable cancer will be used since until these patients are treated they have the same probability of dying. Since these mortality probabilities vary with time they were subtracted from the probabilities of staying in the state i.e. non-dysplastic Barrett's oesophagus to non-dysplastic Barrett's oesophagus. This ensured that all probabilities sum to one.

These transitions represent yearly probabilities. To convert these into monthly transitions to fit the cycle length the following formula will be used where p is the yearly probability (Briggs et al 2003):

$$1\ month\ probability = 1 - e^{((\ln 1 - P) * (1/12))}$$

Hence, the transition matrix for natural history is presented in table 4:

Table 6 Natural history transition matrix (monthly)

	NBO	Bar	LGD	HGD	Cana	Cans	Dead
NBO	#	0	0	0	0	0	Age
Bar	0.001	#	0.002	0	0	0	Age
LGD	0	0.011	#	0.003	0	0	Age
HGD	0	0	0.004	#	0.006	0	Age
Cana	0	0	0	0	0.946	0.013	Age
Cans	0	0	0	0	0	0.881	0.119
Dead	0	0	0	0	0	0	1
# = 1- other states; NBO = no Barrett's oesophagus; BAR = non-dysplastic Barrett's oesophagus; LGD = low grade dysplasia; HGD = high grade dysplasia; cana = asymptomatic cancer; cans; symptomatic cancer							

It does have some limitations. The main issue affecting external validity is that it only allows a step wise progression. So transitions from no dysplasia to high grade dysplasia are not possible. From the other papers and from the GDG this appears to lack face validity.

The method to do so is also the preferred method to incorporate uncertainty into a Markov model with several states, by using the Dirichlet distribution in a Bayesian framework.

The Dirichlet distribution is a multinomial equivalent of the beta distribution (a probability distribution that is bounded by 0 and 1). This allows us to place distributions on a parameter while maintaining the axiom of probabilities (summing to one).

The Bayesian approach is intuitively simple. It allows us to calculate a probability based not only on our understanding of the probability distribution

of an event but also on any prior information we have access to. These two parts are technically called the posterior and the prior.

In this case prior beliefs can be included that the transitions that have no study evidence for can occur. For more details on the method please see Briggs et al 2003.

In this case the priors should not be completely uninformative, as the prior belief is that Barrett's can develop without being a stepwise progression. Therefore, for transitions where data is available uninformative priors will be used and for those where no data is available a more informative will be used, thereby allowing these transitions. The effect of the chosen priors on the cost effectiveness will be explored via sensitivity analysis.

The chosen priors are presented in table 7.

Table 7 Priors for natural history transition matrix

	NBO	Bar	LGD	HGD	Cana	Cans	Dead
NBO	0.12	0.24	0	0	0	0	0
Bar	0.12	0.12	0.12	0.24	0.24	0	0
LGD	0.24	0.12	0.12	0.12	0.24	0	0
HGD	0.24	0.24	0.12	0.12	0.12	0	0
Cana	0	0	0	0	0.12	0.12	0
Cans	0	0	0	0	0	0.12	0.12
Dead	0	0	0	0	0	0	0

NBO = no Barrett's oesophagus; BAR = non-dysplastic Barrett's oesophagus; LGD = low grade dysplasia; HGD = high grade dysplasia; cana = asymptomatic cancer; cans; symptomatic cancer

A value of 0.24 was used for transitions where no data is available but is expected to occur. The reason why the transitions from no Barrett's oesophagus are uninformative is that there is no data indicating that people who were previously had Barrett's oesophagus are more likely to develop cancer or go straight to a severe state of Barrett's. Information from Inadomi et al 2003 suggests that it is possible for people to develop Barrett's again. A value of 0.12 was chosen for the uninformative priors because of a calculating error in excel (the small numbers involved resulted in num! errors) meant

smaller priors were not possible. This was resolved by increasing the size of the observed data by multiplying them by 100 to maintain the relative difference between the priors and observed data.

Hence, using the probabilities from Garside et al 2006 and the Dirichlet framework the following transition matrices for the natural history (table 8) will be used. These represent the yearly transitions, which are then converted to monthly probabilities in the model

Table 8 Final transition matrix - natural history

	NBO	Bar	LGD	HGD	Cana	Cans	Dead
NBO	#	0.0236	0	0	0	0	Age
Bar	0.0405	#	0.0515	0.0235	0.0235	0	Age
LGD	0.0235	0.1486	#	0.0569	0.0235	0	Age
HGD	0.0235	0.0235	0.0696	#	0.0913	0	Age
Cana	0.0000	0.0000	0.0000	0.0000	#	0.1630	Age
Cans	0	0	0	0	0	0.2155	0.7845
Dead	0	0	0	0	0	0	1

= 1- other states; NBO = no Barrett's oesophagus; BAR = non-dysplastic Barrett's oesophagus; LGD = low grade dysplasia; HGD = high grade dysplasia; cana = asymptomatic cancer; cans; symptomatic cancer

5.2.2 Post surgery

For the post surgery states data from Garside et al 2006 is used as the main source of information, however, data from Prasad et al 2007 and 2009 is used to inform the probability of developing cancer after surgery for HGD. In Garside et al 2006 the two recurrence rates were dependant on whether the cancer was detected via surveillance or no surveillance. It shall be assumed that the surveillance rate is equivalent to asymptomatic cancer and the no surveillance arm to symptomatic cancer. The resultant matrix is presented in table 9. The priors used were all uninformative.

Table 9 Post surgery well transition matrix

	Well (asymp)	Well (HGD)	Well (symp)	Cancer (asymp)	Untreatable cancer	Complications	Dead
Well (asymp)	#	0	0	0	0.092	0	Age
Well (HGD)	0	#	0	0	0.01	0	Age
Well (symp)	0	0	#	0	0.26	0	Age
Cancer (asymp)	0	0	0	#	0.143	0	Age
Untreatable cancer	0	0	0	0	0.22	0	0.78
Complications	#	0	0	0	0	0	Age
Dead	0	0	0	0	0	0	1
# = 1- other states; NBO = no Barrett's oesophagus; BAR = non-dysplastic Barrett's oesophagus; LGD = low grade dysplasia; HGD = high grade dysplasia; cana = asymptomatic cancer; cans; symptomatic cancer							

However, it was assumed that all transitions currently labelled as being not possible remained so. For example it is impossible for someone to have complications without first having surgery.

5.2.3 Treatment effect

The values for treatment are based on the conclusions of the clinical review (Please see full guideline document for details of the clinical review). The key outcomes searched for were complete ablation of dysplasia (this includes NBO and BO) and complete ablation of Barrett's (this only includes NBO). The clinical review concluded that a evidence synthesis was not appropriate given the quality of the papers. Therefore, the highest quality paper was chosen that reported the key outcomes. Details of the values were chosen are outlined below.

5.2.3.1 Endoscopic mucosal resection (EMR)

The clinical section detailed a number of papers of generally poor quality. The best of these papers was Ell 2007. Details of this study are presented in the main evidence tables.

The conclusion of the paper was that the mean number of EMR received was 1.8 and on average 99% of patients achieved complete ablation of dysplasia. The GDG considered that this value was an overestimate since it was carried

out in a highly specialised setting. Therefore, it was lowered to 85% for the base case. In addition, this paper was of low quality. Therefore, this value is associated with considerable uncertainty. This shall be explored in sensitivity analysis by altering the Bayesian priors. This will allow explicit consideration of how the uncertainty affects the results by varying the priors.

5.2.3.2 Oesophagectomy

The clinical estimates for surgery are based on the assumption that if done correctly it should completely cure the Barrett's oesophagus, however, evidence from the GDG suggests that it is associated with a mortality of approximately 1%. These are assumptions; are consistent with the British Thoracic Surgeon's guidelines (Fernando et al 2009) estimates of mortality. There is additional data in a PDT paper identified by the clinical review. Prasad et al 2007 indicated that in 61 patients with HGD, there were no deaths due to surgery and only 1 death due to complications although 9 patients were readmitted due to complications (12.6%), Prasad et al 2009 indicated that 3 people were readmitted due to surgical issues (6.5%) therefore the estimate to be used in the model will be 7% in the model. Uncertainty in these values was captured using the Dirichlet distribution.

5.2.3.3 Surgery for cancer

Surgery for asymptomatic, symptomatic and perforations were all assumed to have the same outcomes. This was considered reasonable since once a person is considered suitable for surgery they should be expected to have similar outcomes from surgery. The probability or mortality and complications are the same as for oesophagectomy.

The proportion considered untreatable with surgery is an important variable since it affects the number going to the expensive untreatable cancer state. Estimates from Garside et al 2006 were used as the source for the proportion of people with asymptomatic (5%) and symptomatic (50%) cancer who are considered unsuitable for surgery. These estimates are used to calculate the number going to the untreatable cancer state and in the calculation of the

costs. Uncertainty was captured using a simple uniform distribution between higher and lower values since no information on the distribution was available.

5.2.3.4 Ablation

- RFA

The estimates for RFA were based on the results of the RCT by Shaheen et al 2009. This was the highest quality study included in the review and provides results for the relevant population. (See clinical section). The relative risk from this paper will be applied in the model (4.25RR) without alteration. According to Shaheen et al 2009 a maximum of 4 treatments could be given and the mean number was 3.5.

- PDT

The estimates for PDT were based on the results of the RCT by Overholt 2005, 2007. This was the highest quality study included in the review and provides results for the relevant population. The relative risk of complete eradication of dysplasia from this paper will be applied in the model (4.109RR) without alteration. According to Overholt on average 3 treatments were given. It is assumed a maximum of five could potentially be given at one treatment setting.

- EMR plus APC

The estimates for EMR plus APC were based on the results of the case series by Pouw et al 2008 and Peters et al 2006. Pouw et al 2008 was the only study with 12 months follow up to record the outcome complete eradication of Barrett's. However, Peters et al 2006 reported the eradication of HGD was 100%. This appears unlikely to occur in clinical reality therefore the midpoint between Pouw et al 2008 estimate of complete eradication of Barrett's 67.65% and the 100% from Peters et al 2006 was used. This gives a value of 83.825% for the eradication of dysplasia. It was assumed that on average 1 EMR is given and according to Pouw et al 2008 a mean of 3.5 APC were given. Therefore, a mean of 3 is assumed.

- EMR plus RFA

The estimates for EMR plus RFA were based on the results of the case series by Sharma et al 2009 and Gondrie et al 2008a;2008b, Beaumont et al 2009, Pouw et al 2009, Pouw et al 2010 and Smith et al 2006. These are the only studies of EMR plus RFA. The estimate of complete eradication of dysplasia is 79% to 100%. The mid-point was used in the mode of 89.5%. For the complete eradication of Barrett's the estimate was 83.3%. No data from the papers was available, but estimates from the GDG suggested that they would give on average 1 EMR and then 2 to 3 RFA.

- EMR plus PDT

The estimates for EMR plus PDT were based on the results of the case series by Behrens 2005; Buttar 2001; Mino-Kenudson 2005; Van Hillegersberg 2003; Wolfsen 2004. The study only reported the complete eradication of Barrett's outcome of 50-100%, the midpoint of 75% was used in the model. To calculate the outcome complete eradication of dysplasia an assumption had to be made. Therefore, an assumption shall be made that it is as effective as EMR + RFA. The GDG noted that on average they give 1 EMR and then 3 to 5 PDT treatments.

5.2.4 Treatment transitions

The usual way of incorporating clinical data into a model is to use the relative effect of the treatments to calculate how many more people would regress to NBO and BO from HGD than if left naturally. However, for EMR and EMR combined with RFA, APC and PDT there is no estimate of relative effect. Using the absolute results would lead to an overestimation. Therefore, the control arm estimate from Overholt et al 2005;2007 will be used for all treatments this gives the following relative risks for the treatments.

Table 10 Relative risk calculations

Treatment	Intervention	Placebo	Relative risk
EMR	85%	14.3%	5.95
RFA	81%	19%	4.25
PDT	58.7%	14.3%	4.11
EMR plus RFA	89.5%	14.3%	6.27
EMR plus APC	83.8%	14.3%	5.87
EMR plus PDT	89.5%	14.3%	6.27

The next issue is how many people transit to no Barretts oesophagus relative to non-dysplastic Barrett's oesophagus. For RFA, PDT, EMR plus RFA and EMR plus APC the proportions who achieve complete ablation of Barrett's and of dysplasia are reported in the studies. For EMR plus PDT the results from EMR plus RFA were extrapolated across since they are both of similar efficacies.

Table 11 Percentage allocated to No Barrett's and Non-dysplastic Barrett's

Treatment	No Barrett's	Non-dysplastic Barrett's
EMR	0.010	0.990
RFA	0.738	0.262
PDT	0.563	0.438
EMR plus RFA	0.833	0.167
EMR plus APC	0.676	0.324
EMR plus PDT	0.833	0.167

These figures were applied to the proportion of people having complete ablation of dysplasia.

The main complication for the ablative therapies was perforations. These were extracted from the clinical studies. The sources for the estimates are presented below in table 12:

Table 12 Probabilities for perforations

	Perforations	Source
EMR	0.02	Midpoint estimate from Inoue et al 2008 and Lopez et al 2007
RFA	0.02	Shaheen et al 2009
PDT	0.01	Assumption
EMR and RFA	0.04	Pouw et al 2009a:2009b
EMR plus APC	0.03	Peters et al 2008
EMR plus PDT	0.01	Assumption

As all the effectiveness estimates comes from trials with duration of more than 12 months the yearly transition probabilities are presented in table 13:

Table 13 Treatment transition matrix

	NBO	Bar	LGD	HGD	Perforations
Natural history	0.028	0.028	0.061	0.80	0
EMR	0.00	0.33	0.061	0.58	0.02
RFA	0.17	0.06	0.061	0.68	0.02
PDT	0.13	0.10	0.061	0.70	0.01
EMR and RFA	0.29	0.06	0.061	0.55	0.04
EMR plus APC	0.24	0.05	0.061	0.64	0.03
EMR plus PDT	0.22	0.11	0.061	0.59	0.01
NBO = no Barrett's oesophagus; BAR = non-dysplastic Barrett's oesophagus; LGD = low grade dysplasia; HGD = high grade dysplasia;					

These estimates will be explored in sensitivity analysis.

5.2.5 Adverse events

The only other adverse event included is the probability of stricture. The estimates for this event are presented below in table 14 with references to the clinical sections. The upper limits were also derived from the literature; lower limits were assumed to be zero.

Table 14 Adverse event probabilities and source

Treatment	Stricture prob.	Lower	Upper	Reference
EMR	0.007	0	0.125	Inoue et al 1998
RFA	0.024	0	0.048	Shaheen et al 2009
PDT	0.368	0	0.5	Overholt et al 2005;2007
EMR plus RFA	0.042	0	0.173	Pouw et al 2009;2010
EMR plus APC	0.256	0	0.583	Peters et al 2006
EMR plus PDT	0.083	0	0.294	Pacifico et al 2003

The only additional quality of life estimate included was photosensitivity reactions for PDT and EMR plus PDT. These estimates are presented below in table 15.

Table 15 Photosensitivity probabilities

Treatment	Photosensitivity prob.	Lower	Upper	Reference
PDT	0.690	0.18	1	Overholt et al 2005;2007
EMR plus PDT	0.083	0	0.118	Pacifico et al 2003

6 Quality of life section

Ideally a full systematic review would be carried out to identify health related quality of life (HRQoL) studies and appropriate values for inclusion in a health economic model. However, due to constraints of resources and time this is not possible. Therefore, a search will be carried out for quality of life studies and examination/critique of quality of life data included in cost effectiveness analyses identified in section 4 and the two surveillance studies identified in section 5.

6.1 Literature search

The search that was carried out at the beginning identified 4 papers that examined quality of life in patients with Barrett's oesophagus: Chin Hur et al 2006, Richards et al 2003, Ofman et al 2003 and Hur et al 2005. Of these papers only Hur et al 2006 identified utilities appropriate for inclusion in an economic analysis as they corresponded to health states. A systematic review

by Crockett et al 2009 was identified that included Hur et al 2006 and included 3 additional studies not identified originally with values that could be applied to health states in an economic model: Gerson et al 2005 & 2007 and Fisher et al 2002.

6.1.1 Cost effectiveness studies

For details on the source of utilities in the 8 cost effectiveness studies please see the evidence tables in section 13.3. The main studies referenced were Provenzale et al 1994, Provenzale et al 1999 and De Boer AG et al 2002. Only Shaheen et al 2004 carried out de novo work in eliciting new values from patients. Additional studies referenced were: Blazeby et al 2000 and Gerson et al 2000

Provenzale 1994 and 1999 were considered as part of the review of natural history data; however, due to the structure of the models they were not considered appropriate. The reason these studies were not identified by the original search is because the papers are not primarily about Barrett's oesophagus, but related conditions or treatments such as oesophagectomy.

6.1.2 Surveillance studies

The chosen surveillance studies (Garside et al 2006 and Inadomi 2003) utilised two different methods. Garside et al 2006 developed descriptions of the conditions with clinicians and patients and then got a sample of the general public to value these health states using a time trade off methodology.

Inadomi et al 2003 used values from Provenzale 1994 and 1999 for post surgery and assumed perfect health for all other states apart from cancer which was obtained by authors consensus.

6.1.3 Review of literature

Crocket et al 2009 primarily reviewed the published literature on quality of life data collected for Barrett's oesophagus. The review considered numerous methods for collecting quality of life and also specifically looked at quality of life linked to health states.

Of the remaining values presented they examine different aspects of the treatment of Barrett's oesophagus with very little overlap with the states considered. The most relevant to the health economic model are those of Gerson et al 2007b and Hur et al 2006.

Gerson et al 2007b used visual analogue scale and time trade off methods to obtain health related quality of life estimates from people with Barrett's oesophagus. These results suggest that as Barrett's oesophagus progresses health related quality of life decreases quite steeply from 0.91 for no Barrett's oesophagus to 0.77 for HGD.

Hur et al 2006 used standard gamble techniques on people with Barrett's oesophagus to provide data on post treatment quality of life. The results indicate indicating only very minor decrements from treatment including surgery. For example no Barrett's oesophagus health related quality of life is 0.95 while post surgery it is 0.92.

Gerson et al 2005 used a visual analogue scale, time trade off and standard gamble to examine the effects on taking medication. No medication health related quality of life was 0.93 and on medication was 0.95 according to standard gamble methods. Fisher et al utilised a 10 point scale using the visual analogue scale only. This indicated that as severe health states were associated with lower health related quality of life than less severe health states.

Most of the cost effectiveness studies include references to Provenzale et al 1994 and 1999. Provenzale et al 1994 examined the morbidity associated with endoscopy, endoscopy with complication, elective surgery and emergency surgery. Endoscopy was based on expert opinion and the others on the US government's 1989 Federal register. The long term morbidity associated with oesophagectomy was 0.8 estimated by an author's assumption that patients regard living 10 years with an oesophagectomy to be equivalent to living 8 years in perfect health. In Provenzale et al 1999 the morbidities associated with endoscopies came from US government figures. The long term morbidity was calculated by time trade off by asking a group of patients with Barrett's

oesophagus who had undergone surgery for HGD or cancer more than one year ago from Duke University. The median value from this group of patients was 0.97 (inter-quartile range of 0.83-1).

De Boer et al 2002 obtained visual analogue scores and standard gamble scores from 93 patients in the Netherlands who had surgery for cancer of the oesophagus. They were asked to value their own current health state and of various descriptions of health states. It was not clear who had developed the health states. This paper had quality of life values for post surgery, post surgery and recovering, in hospital without complications, in hospital with complications, recurrence and unresectable.

Shaheen et al conducted a new quality of life analysis to supplement their analysis. Utilities for living in states of endoscopic surveillance were derived from 56 veterans with Barrett's oesophagus undergoing surveillance at Durham Veterans' Affairs Medical Center using only the visual analogue scale. This is an inappropriate instrument to use alone since it can lead to overestimation of health related quality of life in comparison to choice based instruments such as the time trade off.

6.1.4 Quality of life – Model

None of the studies are in complete accordance with NICE methods. NICE recommends the use of the Euroqol 5 dimensions (EQ-5D) or another generic tool which enables patients to describe their health states and the public values their health states. In addition, there is no one set of values that can be used for the entire model. There are also potential issues of using different values from different sources which may lead to inconsistency. For example time trade off and standard gamble techniques have a tendency to produce different estimates for the same health states. To minimise these issues studies will be chosen that are closet to NICE methods and also share similar populations and methods of eliciting and valuing health states.

Garside et al 2006 obtained the most robust source of utility data since the estimates were described by patients and valued by the public. In addition, a

combined visual analogue scale and time trade off methodology was used, again in line with NICE methods. The study that most resembles Garside et al 2006 is Gerson et al 2007b which similarly used visual analogue scale and time trade off methodology; however, the states were valued by patients and not the UK public. These values were collected from patients with Barrett's oesophagus and they were asked to value health states that described the condition and the risk of cancer. This could potentially be misleading as patients are valuing a potential risk. Finally the only other paper that uses a choice based instrument is De Boer et al 2002; however, time trade off is preferred to standard gamble. These three studies will therefore provide the majority of utility data. Additional sources will be used if there are no suitable estimates.

There is an issue in that since all used visual analogue scale and time trade off methodology to value health states it means that they could all have different baselines for population norms. In Garside et al 2006 they use EQ-5D figures for a baseline and Gerson et al 2007b assumes baseline to be 1. Combination of these estimates may result the incremental differences being inconsistent. To minimise this issue the utilities derived from the studies will be used as weights on the average EQ-5D score for this population (60 year olds plus). UK population norms for EQ-5D (Kind et al 1999) indicates that this value is approximately 0.8. Therefore, all values will be relative to this unless otherwise stated.

6.1.5 Barrett's oesophagus natural history

The most robust estimates for the natural history states are from Garside et al 2006 who used descriptions developed by patients but valued by the UK public. This is in line with NICE methods. Therefore, these shall be used for the majority of the utilities. However, there are a number of assumptions and values that appear either counterintuitive or lack face validity.

The first issue concerns the progression of Barrett's oesophagus from non dysplastic Barrett's oesophagus to high grade dysplasia. Garside et al 2006 assumes that it remains constant while Gerson et al 2007b demonstrated that

quality of life decreased with progression. The GDG considered that there was a decrease in quality of life associated with the progression of Barrett's oesophagus. What is difficult to assess is whether this is because of the perceived risk of cancer or their underlying condition. Given the GDG's opinion that quality of life is negatively associated with Barrett's severity the estimates from Gerson et al 2007b will be used as the base case data and then the estimates from Garside et al 2006 will be used as a sensitivity analysis.

The second is the quality of life for asymptomatic cancer. Garside et al 2006 assumed that once asymptomatic cancer was diagnosed a person's utility was 0.875. This value is higher than a post surgery well (0.863) and person without Barrett's oesophagus (0.8). In the model once a person is diagnosed with cancer they are given treatment, therefore, someone with asymptomatic cancer will be assumed to have the same utility as someone with HGD. This is because the cancer is still asymptomatic and therefore is unlikely to affect the quality of life of the person until it is detected. In addition, this is in line with the estimate from Gerson et al 2007b.

6.1.6 Ablation treatment

The GDG did not consider that treatment would be associated with a major decrement to health outside of adverse events. Often the effects were mild such as sore throats and so on. Therefore, it seems reasonable to not include these in the modelling. People will therefore only experience the same quality of life as someone with HGD.

6.1.7 Surgery and post surgery quality of life

For post-surgery quality of life there is a clear indication that post-surgery quality of life is not a major detriment to quality of life. Garside et al 2006 assumes a utility of 0.863 which is higher than the values for those with dysplasia. This does not seem unreasonable since people will not be concerned about their condition progressing to cancer.

However, none of the papers presented evidence on the effect of surgery in the short term. The GDG considered the quality of life of those post-surgery. It noted that there was strong evidence to suggest that quality of life after surgery is initially affected quite significantly and then the patient adapts and quality of life returns to pre-surgery levels. It is advised that JM Blazeby has done work in this area which would be useful to examine.

On advice of the GDG five studies by Blazeby were identified: Kavadas et al 2004, Barbour et al 2008, Rutegard et al 2008, Blazeby et al 2005, Djarv et al 2008. While the search was unsystematic it should provide enough information for the purposes of the analysis.

The studies suggest that there is an initial decrement to quality of life post surgery which is then gradually regained as the patient adapts. Therefore, it would appear sensible to model the initial decrement as part of the treatment and then return to their baseline health related quality of life thereafter.

Therefore only the initial decrement from surgery will need to be calculated. In the identified studies data were collected using EORTC QLQ-30, a quality of life instrument designed for cancer trials. In their current form they cannot be used in the model as they are not on a scale 0 to 1. However, there is an algorithm that converts these values into EQ-5D stated in McKenzie et al 2009. The authors of this paper concluded that their algorithm is valid but that more evidence is required before it can be the recommended method for conversion. This conversion has been used in a previous NICE appraisal and was considered appropriate (Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia, NICE technology appraisal in progress). Therefore, it shall be used in this analysis to estimate the decrement of surgery. The Barbour et al 2008 study provides EORTC QLQ-30 data for baseline and 6 months post surgery. In section 13.7 the details of the conversion of the EORTC values to EQ-5D are presented. This evidence suggests that the quality of life difference is 0.1245 on the EQ-5D scale. This shall therefore be subtracted this from the patient's baseline score i.e. if they are having surgery for asymptomatic cancer this will

be subtracted from 0.77 to produce 0.49. The utility value of 0.49 will be applied to the surgery state which means that the disutility lasts for one month.

6.1.8 Quality of life – Adverse events

The model only considers major adverse events including perforation, strictures and photosensitivity reactions.

6.1.9 Stricture

Of the cost-effectiveness analyses identified only Das et al 2009 and Vij et al 2004 include quality of life decrements associated with adverse events. Das et al 2009 assumed that for strictures related to ablative therapy that a person's quality of life would be 0.97 representing a decrement of 0.03 from normal health, but unchanged from LGD/HGD. This estimate was obtained from Provenzale et al 1999; it is assumed that they have extrapolated the quality of life for post surgery to this state. It is unclear why this should be the case, but parallels could be drawn since it involves an operation involving endoscopic therapy. For Vij et al 2004 the utility for stricture after PDT was assumed to be 0.97 for patients with meta, normal or high dysplasia. This estimate was based on an author's consensus.

For the model it does not seem reasonable to extrapolate the disutility associated with post surgical state to that of stricture treatment.

One option would be just to assume that there is no quality of life impact only a cost impact. The alternative is to extrapolate from a therapy that is similar. Surgery is too severe, however endoscopy is more comparable. Hur et al 2006 report that those undergoing intensive endoscopic surveillance for HGD had a utility of 0.90 which represents a decrement of 0.05 from normal health or a 5% decrease. The limitations of this choice are that this represents continual endoscopic investigations rather than a single procedure; however, it is possible that the cumulative effect is similar to a single dilation procedure. So in the model a midpoint of 0.04 will be used and estimates will range from

0.03 to 0.05. This will be implemented as 4% from baseline (0.80) resulting in 0.80*0.04=0.032.

6.1.10 Photosensitivity reactions

There are no estimates of health related quality of life reported in the literature currently identified for photosensitivity reactions. However, treatment is often over the counter pain killers therefore it is unlikely to be a major adverse event. Therefore, for the base case same value as for strictures will be used.

6.1.11 Perforations

There are no estimates of health related quality of life for perforations reported in the literature. However, the treatment of perforations is currently surgery which is similar in severity and effect on patients as oesophagectomy. Therefore, the decrement identified for surgery will be extrapolated to this event.

6.1.12 Final QOL values

Table 16 Final health related quality of life estimates

State	Mean Value	SE	Reference
Baseline (55-65)	0.8	N/a	UK population norms
NBO	1.00	n/a	Assumption
Bar	0.910	0.13	Gerson et al 2007b
LGD	0.850	0.12	Gerson et al 2007b
HGD	0.770	0.14	Gerson et al 2007b
Asymptomatic cancer	0.770	0.14	Assume same as HGD
Symptomatic cancer	0.675	0.19	Garside et al 2006
Well	0.863	0.016	Garside et al 2006
Complication	0.5	0.020	Garside et al 2006
Untreatable	0.4	0.042	Garside et al 2006
EMR & RFA	0.770	0.14	Gerson et al 2007b
Surgery for asymptomatic cancer	0.49	0.14	Section 13.7
Surgery for symptomatic cancer	0.414	0.19	Section 13.7
Surgery for perforation	0.49	0.14	Section 13.7
Surgery for HGD	0.49	0.14	Section 13.7
Stricture	-0.032	0.042	Hur et al 2006
Photosensitivity reaction	-0.032	0.042	Same as stricture
# = 1- other states; NBO = no Barrett's oesophagus; BAR = non-dysplastic Barrett's oesophagus; LGD = low grade dysplasia; HGD = high grade dysplasia			

7 Resource use

7.1 Literature search

From the initial search five studies were identified that examined resource use in Barrett's oesophagus. Eloubeidi et al 1999, Amonkar et al 2002, Achkar et al 1988 and Ofman et al 2003. Arguedas et al 2001 was excluded since it was a review article of cost effectiveness results. All these studies were from a US perspective. A brief review is produced below in table 17.

Table 17 Review of resource papers

Study and year	Condition	Country	Source of cost information	Cost estimate
Achkar et al 1988	Barrett's oesophagus	USA	Unclear	Endoscopy - $400
Eloubeidi et al 1999	Barrett's oesophagus	USA	Cost data from Durham Veterans Affairs Medical centre	Average cost /month ($) Clinic visits – 6.06 EGDs – 32.21 Medication – 65.12 Total – 103.39
Amonkar et al 2002	Barrett's oesophagus	USA	Published government costs	Endoscopy - $310.23 Blood pathology - $4.69 Cytology pathology – $8.34 Surgical pathology – $34.08 Radiology - $3.99 Pharmacy costs (year) $609.61
Ofman et al 2003.	Acid related disorders including Barrett's oesophagus	USA	Orlando health care group database	Total cost of treatment at 6 months mean $220.30

These studies are not directly applicable to the UK setting since they are all based in the USA.

7.1.1 Cost effectiveness studies – Ablation and natural history

Section 13.8 outlines the source and value of costs used in the cost effectiveness models for ablation and natural history studies that were selected for information on transitions.

There are surprisingly few references. The references mentioned are the CMS, Provenzale et al 1994 and 1999, Soni et al 2000, Gorelick et al 2001. Other cost sources include Soni et al 2001, Canadian reference costs and individual hospital costs.

- CMS costs represent the US version of UK reference costs. Therefore they are subject to the same limitations as UK reference costs.

- Gorelick et al 2001 was a US study that examined the cost of oesophagogastroduodenoscopy (EGD) and compared two versions in terms of costs. It found that small calibre EGD cost $462 and conventional EGD $587.
- Provenzale et al 1994 the costs were obtained from the New England Medical Centre specifically the clinical cost manager 1990 and hospice charges, Massachusetts' 1990.
- Provenzale et al 1999 costs were obtained from Duke Medical Centre 1995 and hospice charges, North Carolina 1996.
- Soni et al 2000, obtained their costs from CMS and the purchasing officer of their hospital pharmacy.

The issue, therefore, is how applicable US reference and hospital costs are to the UK. There are a number of issues around applying US costs to a UK setting. The CMS costs are likely to suffer from the same issues as NHS reference costs. However, they have been in use for longer and as the US health service is organised around the pay per service they could be viewed as potentially more accurate. But, US costs are generally higher than similar costs in the UK. In addition, it is often suggested that US are more resource intensive than is necessary and may be misleading. Therefore, there is a possibility that these costs represent an overestimation. Therefore, UK specific costs will be used.

For the UK the reference costs are the main publically collected resource sets. A potential limitation with NHS reference costs is whether they accurately represent the underlying costs involved. Therefore it's important to consider the constituent parts of the health resource groups. These will be considered when going through the specific costs.

7.1.2 Specific costs for the model

The main cost inputs that require consideration include:

- Surgery for asymptomatic and symptomatic cancer
- Surgery for HGD
- Complications

- Treatment for perforation
- Treatment of stricture – dilation
- Endoscopy and biopsy
- EMR
- Ablation
- PPIs
- Untreatable cancer
- Post surgery well

Each of these costs will now be considered in detail below.

7.1.2.1 Surgery

As has been discussed before in this model it is assumed that there are two main types of surgery, one as a preventative treatment the other will be to treat cancer. Both of these require a full oesophagectomy. For oesophagectomy patient advice leaflets from Addenbrooke's and Royal and Devon Exeter hospital trusts indicated that the average length of stay would be 10-14 days. The excess bed days codes provide a cost of £176 per day. The cost code that best matches surgery for cancer is FZ01B - Complex oesophageal procedures 19 years and over without cc at £6706 per procedure with average length of stay of 8.69 days. This procedure code includes various types of surgery which all appear to be of a similar resource magnitude. Therefore, an average of 12 days for the procedure will be assumed ergo the calculation is:

((12-8.69)*176)+6706 = £7288.56.

The inter-quartile range around this value will be assumed to be the upper and lower values of the reference costs included in the calculation. The calculations are summarised below.

((10-8.69)*133)+4570 =£4744.23

((14-8.69)*210)+8632 =£9747.1

Surgery for oesophageal cancer is often accompanied by chemotherapy. SIGN guidance indicated that chemotherapy of 5-FUI should be used as neo-adjuvant therapy although it can also be used as adjuvant therapy. The National Oesophago-gastric cancer audit (2008) indicated that 56% of patients with oesophageal cancer in 2005 received chemotherapy. It will be assumed that people receive chemotherapy as part of their surgical procedure and therefore it is delivered in the inpatient setting. This gives us a mean cost of £203 (Band 1 day case drugs) plus delivery cost of £201 for oral chemotherapy according to NHS coding. Combining these gives a total of £404. Multiplying this by 0.56 gives the average cost of chemotherapy in this patient group of £113.8. This total is therefore: £7402.24 (IQR: £4857.91 to £9860.78).

For preventative treatment the chemotherapy will be excluded and the base cost from the NHS reference costs will be used.

7.1.2.2 Cost of proton pump inhibitor (PPI)

Concurrent PPI treatment is often used to control the underlying gastric condition. It has been assumed that the amount of PPI received does not vary with the severity of the condition. Therefore, it can be argued that PPIs could be excluded from the analysis since they will be present in all analysis. However, by including it the difference between those states where PPIs are taken and those where they are not such as cancer is reduced. BNF 58 and electronic Market Information Tool (eMIT) were examined for information on the recommended dosage and price of PPIs. A number of the most common PPIs are now generic and therefore their price varies considerably and there is likely to be local discounts available. EMIT was therefore also searched for a summary of the price PCTs pay for generic treatments. This however ignores any over the counter medication that patients may be taking.

The costs and doses are summarised in section 13.9. The average price is approximately £22 per month which has not changed substantially since the Garside et al 2006. This will be the value applied to the no Barrett's oesophagus, non-dysplastic Barrett's oesophagus, LGD and HGD states. The

states of well post oesophagectomy do not include PPI since there is no longer a need to control stomach acid. It is assumed that patients in the asymptomatic and symptomatic cancer stages contained in the diagnostic categories will stay on PPI until diagnosed and they receive cancer treatment.

7.1.2.3 Complications

The cost of complications was calculated by subtracting the cost of surgery without complications from the cost of surgery with complications. No extra days were included since these should be captured by the average duration of surgery with complications. Therefore, the cost of complications is £2583. (9289-6706 = £2583)

7.1.2.4 Perforation

The treatment for a perforation in surgery although it may be less extensive it is still a serious surgery. However, the cost for this procedure is captured within the complex oesophageal procedure cost code.

The issue is that if a differential is needed between this procedure and the process of removing a cancer. It will be assumed that the time and resources required are likely to be similar and in addition, unlikely to differ greatly. However, whether the treatment is elective or non-elective is likely to be different. As this is the potential complication of surgery the non-elective cost will be utilised for this procedure. This provides a cost of £3819. No excess bed days need to be considered as the duration of treatment is 9.25 days.

7.1.2.5 Dilation

Dilation as a procedure is covered by FZ24C - Major Therapeutic Open or Endoscopic Procedures 19 years and over without complications, in particular G15.2. However, it is likely patients would be kept overnight for observation especially for potential perforation or any further complications. Therefore, the non-elective inpatient cost will be used; the reason for non-elective is because it is an adverse event of treatment. This provides a cost of £703.

7.1.2.6 Endoscopy

The cost of endoscopy is provided by the NHS cost code FZ03A - Diagnostic and intermediate procedures on the upper GI tract 19 years and over, with a corresponding cost of £459. According to the GDG opinion two pathologists are required to examine the sample. The cost of pathology is given by code DAP824 (£29) this is multiplies by 2 and added to the endoscopy cost. This produces a cost of £517.

7.1.2.7 EMR and ablation

The costs associated with EMR are represented by cost code FZ24C - Major Therapeutic Open or Endoscopic Procedures 19 years and over without CC. On advice of the GDG it is likely that this procedure would be classified as a day case therefore giving a cost of £521. To this the cost of carrying out a pathology test (with two pathologists) to ascertain the success of the procedure s added. This brings the cost to (521+58) = £579. An important consideration is if there are any capital costs or consumables that would not be covered by this cost code.

It is unlikely there would be any significant capital costs as all the equipment is standard and required to carry out an endoscopy. There does not appear to be any expensive consumables as well. Therefore, only the cost code for EMR will be used.

For ablation the costs are represented by the cost code FZ24C – Major therapeutic open or endoscopic procedures 19 years and over without complications. On advice of the GDG this procedure would be classified as an inpatient stay at a cost of £1135. In addition, the cost of pathology is included. On the issue of capital costs there is likely to be variation depending on where the procedure is being carried out. In specialist centres the reference cost alone is likely to be sufficient because given the number of procedures the centre is carrying out the reference cost should cover issues of depreciation and consumables since contracts are likely to be already in place and economies of scale are likely. However, if the procedure was carried in low

volume centres it is likely that capital costs will need to be included. Therefore, the base case will include them to take into account the potential adoption costs. Information from the GDG indicated that the capital costs for PDT and RFA were approximately equal and that for APC they would be considerably lower. Therefore, the following assumptions were made and are listed in table 18:

Table 18 Capital cost assumptions

Ablative therapy	Capital cost
RFA	£60000
APC	£10,000
PDT	£60,000

These estimates need to be annualised to allow them to be incorporated into the model. By annualising it takes into account depreciation, replacements and residual value. The formula for annualising costs is presented below:

$$E = \frac{K - \left[S / (1+r)^n \right]}{A(n,r)}$$

Where E = equivalent annual cost, K = purchase price of equipment,
S = resale value, r = discount rate (interest rate); n = equipment lifespan;
A(n,r) = annuity ;factor* (n years at interest rate) * The annuity factor converts the present value of the equipment into an annuity, which is a series of equal annual payments.

It is assumed that the resale value of the machine is near zero and that the life span of the machine between 5 to 10 years (a midpoint of 7.5 was used in the model) based on GDG opinion. The results are presented in table 19:

Table 19 Annualised costs

Ablative therapy	Annualised costs
RFA	£9234.30
APC	£1539.05
PDT	£9234.30

The annualised costs were added to the treatment costs and turned into a per cycle cost by dividing it by 12.

For both PDT and RFA there are likely to be expensive consumables for RFA the balloon and catheter are approximately £2000 according to the GDG this was varied between 0 and £5000. For PDT the cost of the photosensitive drugs is the major cost. The cost of the drugs for PDT were calculated by taking a average persons weight (73kg) and multiplying this by the licensed indication for porfirmer sodium, to produce a cost of £1540. This was varied between this and an alternative cost for 5-ALA a drug which from clinical evidence is associated with fewer adverse events but costs on average £2409.

7.1.2.8 Untreatable cancer

This state represents cancer for which further surgical treatment is not possible. Therefore, it includes palliative care and maybe one off treatments such as stenting. Other treatments may include palliative radiotherapy and possibility chemotherapy. There are also the costs of GP and other primary care resources plus potential hospice costs. Given the range of treatments and variation plus the difficulty in obtaining accurate figures two sources of information were consulted. A HTA report by Shenfine et al 2005 on palliative care for oesophageal cancer was considered alongside Garside et al 2006. Shenfine et al 2005 estimated the total hospital cost per patient of palliative care for untreatable cancer at approximately £5000 over 21 weeks. Garside et al 2006 estimated it at £3578 for a 4 week period. However, the Garside estimate was based on the cost for a stent, 4 days in hospital at £250 per day and £1000 of GP and nursing costs. This indicates that the hospital visit

contributes £2578 to the total cost. Multiplied by 5 to make it equivalent to the 21 week cost estimated by Shenfine et al 2005 gives £12890. This appears to be an overestimate. Therefore the £5000 will be used as the basis for hospital costs. However, as Shenfine does not provide a primary care costs the estimate from Garside et al 2006 will be used. The monthly hospital costs are calculated as follows:

(5000/147.71)*30.5 = 1032.43

Plus the £1000 of GP and nursing costs gives £2032.43

7.1.2.9 Post surgery well

For post surgery well information from the GDG suggested that post surgery patients would probably come into clinic twice a year for checkups. Therefore, the cost of an outpatient appointment (FZ03A-Diagnostic and intermediate procedures on the upper GI tract 19 years and over) was used and then multiplied by two to account for two appointments and then divided by twelve to get a monthly cost. This gives a value of £48.09 per month.

7.1.2.10 Distributions of estimates

It's recommended (Briggs et al 2003) that the gamma distribution is the appropriate probability distribution for costs. To fit a gamma distribution the standard error is required for each value. For the values derived from the Garside et al 2006 and other published papers that have stated standard errors these will be utilised in the model. For the reference costs standard errors were calculated since only the mean and quartile values (except the median). There is no agreed method on the appropriate methodology for the calculation of standard errors from the reference costs. The method utilised was to use the solver function in excel to find the variables for the gamma function that produces the relevant estimates of the upper and lower quartile. The final values and break up are presented in table 20. For costs constructed of various components, for each individual cost a standard error was

calculated (for example, for chemotherapy the cost of administration and the drugs was calculated separately).

Table 20 Mean costs and standard errors used in PSA

Variable	Mean cost (£)	Standard error (£)
EMR	521	470.1
RFA	1135	526.84
PPIs	22	5.5
Surgery	6706	3130.23
Surgery for perforation	3819	2987.89
Bed days	176.45	58.48
Untreatable	2032.43	894.5
Well = outpatient visit divided by 6	258.534	147.21
Endoscopy	459	150.57
Complications	2583	580.91
Stricture	703	525.14
Band 1 day case drugs	203	118.25
oral day case	201	102.95
Pathology	29	1.95

8 Assumptions

There is a major assumption made that HGD and intramucosal cancer can be merged into one state. This was considered acceptable by the GDG and the clinical adviser because these patients would be treated clinically in the same way and therefore it would be unnecessary to split into two separate states.

8.1.1 Cycle length

A cycle length of one month was considered appropriate because its short enough that treatment isn't overly long and that it allows transitions to other states in between surveillance periods.

8.1.2 Drop out from surveillance

There is no drop out from surveillance. There is evidence that people (especially those with mild Barrett's oesophagus) that they drop out of regular surveillance programmes. For a base case it is assumed that there is no drop

out from the surveillance programme, however, this will be explored by seeing what happens if surveillance is stopped after a number of years or treatment.

8.1.3 Age dependency

Apart from age dependent variables, all others are independent of time. This was because of a lack of information on the relationship between time and a number of important variables such as the rate of cancer progression. Death rate is age dependant. This is assuming that people with Barrett's oesophagus have the same mortality as the rest of the UK population. This seems a reasonable assumption since there is no evidence of dramatically different life expectancy other than the increased cancer rate.

8.1.4 Treatment of cancer

Surgery is included as the only treatment for perforation and cancer. This was because of the absence of data on alternatives such as chemoprevention. In addition, all patients in all arms are treated with the same alternatives. Therefore, the impact of this on the cost effectiveness is the relative benefit of preventing these events. So the more expensive surgery and detrimental to health related quality of life the more valuable it is to avoid the event.

8.1.5 Misdiagnosis

It is assumed that there was no misdiagnosis with endoscopy. This was following on from the assumption in Garside et al 2006 where it speculated that the underlying data included a degree of misdiagnosis and to include it would double count the number of misdiagnoses.

8.1.6 Post surgery

Post surgery represents a simplified version of reality. There is only one state for well with the only outcomes being death and cancer.

It is assumed that all people who have surgery for HGD cannot have further surgery for adenocarcinoma. This assumption obviously could underestimate the effectiveness of surgery, however, it was considered acceptable by the GDG and clinical adviser.

8.1.7 Retreatment

People can have as repeated treatments. This was incorporated in the model to reflect the possibility that people can be retreated if they progress to HGD again. However, there is no limit on potentially how many people can get treated. Therefore, this assumption will be relaxed in sensitivity analysis whereby after 80 years of age all treatment will be stopped.

8.1.8 No twelve months review of treatment

If the treatment fails after 12 months the GDG stated that this is viewed as a result of not treating appropriately rather than the treatment not working. Therefore, patients often get re-treated in a twelve month period. However, since patients can be treated whenever they progress to HGD this should be avoided.

8.1.9 Cancer

Cancer is detected once it becomes symptomatic, asymptomatic cancer is only detected by endoscopy. This appears to be a reasonable assumption.

8.1.10 Complications only last one cycle

This was considered appropriate since all costs and utilities are considered. However, it may underestimate the potential impact on quality of life.

8.1.11 Strictures are accounted for by a negative decrement

This was to avoid including health states for adverse events and instead allow several decrements for simultaneous adverse events.

8.1.12 Costs based on reference costs

Therefore, there are issues that these costs may not be representative of the true costs of the procedure. However, these are published NHS costs and represent the average NHS costs across the country.

9 Analysis

An incremental cost effectiveness ratio (ICER) has been calculated for each treatment option in comparison to no surveillance. This is because the poor comparative data prevented any meaningful comparison between treatment options.

9.1 Validation

Validating models requires checking the internal and external validity. Internal validity is ensuring that the model is mathematically correct and that all the calculations are correct. All the calculations have been checked by following number in cohort and double checking the calculations.

External validity is the comparing the model results with clinical practice. To do this the incidence of cancer and mortality was calculated. This will be compared with the results of clinical trial evidence and clinical opinion. For survival for surgery a comparison to Prasad et al 2009 will be made and for the ablative therapies respective clinical trials will be consulted.

9.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis will be carried out on a range of variables including all costs and utilities. For transition probabilities we will examine two sets of transition matrices one of the upper values from the literature and another set of lower values. The full matrices are in section 13.10. Costs will be explored by reducing them by 50% and increasing them by 50% to examine its effect. For quality of life alternative assumptions that the severity of Barrett's oesophagus does not affect the person's quality of life will be explored.

9.3 Probabilistic sensitivity analysis

The following sections outline the variables and distributions subject to PSA. The cost effectiveness plane, cost effectiveness acceptability curves and cost effectiveness acceptability frontiers will be presented from this analysis.

All treatment effects were varied using Dirichlet distributions these include natural history, post surgery, surgery and ablative treatments

9.3.1 Utilities

A novel approach will be used for the probabilistic sensitivity analysis for utilities. Since the utilities for the health states decrease with the severity of the condition it will be necessary to ensure that in any PSA analysis this remains true otherwise counterintuitive results will be produced. Therefore, beta distributions of the differences between the estimates will be used to ensure that the probabilistic results remain consistent. Table 21 outlines the utilities that are varied according to their difference. The standard error of the difference was calculated using the following formula:

$$SE(of\ difference) = \sqrt{(\left(\frac{sd^2}{n_a}\right) + \left(\frac{sd^2}{n_b}\right))}$$

Where sd = the standard deviation of the source population, n = the size of the sample. The data came from Gerson et al 2007b and Garside et al 2006.

Table 21 PSA calculations for quality of life

State	Mean	Standard error	Difference	Standard error of the difference	Distribution	Alpha	Beta
No Barrett's oesophagus	1.000	1.000	NA	NA	NA	NA	NA
Non dysplastic Barrett's oesophagus	0.910	0.130	0.09	0.021	Beta	17.36	175.49
Low grade dysplasia	0.850	0.120	0.06	0.028	Beta	4.27	66.81
High grade dysplasia	0.770	0.140	0.08	0.029	Beta	6.85	78.74
Asymptomatic cancer	Same as HGD						
Symptomatic cancer	0.675	0.032	0.095	0.023	Beta	15.75	150
Untreatable cancer	0.400	0.042	0.275	0.007	Beta	1031.06	2718.24

Table 22 outlines the utilities that were assumed to be independent of the other values.

Table 22 quality of life estimates in model

State	Mean	Standard error	Distribution	Alpha	Beta
Ablation	0.770	0.140	Beta	6.19	1.85
Post surgical well	0.863	0.016	Beta	397.71	63.14
Complication	0.500	0.003	Beta	19999.5	19999.5
Surgery	0.490	0.140	Beta	5.76	5.99
Stricture	0.031	0.042	Beta	0.83	19.94
PDT photosensitivity	0.031	0.042	Beta	0.83	19.94

9.3.2 Costs

Table 23 outlines the costs and standard errors that were modelled using a Gamma distribution

Table 23 PSA Gamma distribution of costs

	Mean	Standard error	Alpha	Beta
EMR	521	244.206	4.552	114.466
RFA	1135	526.840	4.641	244.546
APC	1135	526.840	4.641	244.546
PDT	1135	526.840	4.641	244.546
PPI	22	5.500	16.000	1.375
Surgery	6706	3130.225	4.590	1461.125
Surgery perforation	3819	2987.89	1.634	2337.645
Surgery cancer	6706	3130.225	4.590	1461.125
Excess day cost	176.447	58.483	9.103	19.384
Untreatable cancer	2032.428	894.500	5.163	393.682
Endoscopy	459	150.570	9.293	49.393
Complications	2583	267.059	93.548	27.611
Band 1 day case drugs	203	118.25	2.947	68.877
Oral day case	201	102.953	3.812	52.733
Pathology	29	20.782	1.947	14.893
Outpatient visit	258.534	147.214	3.084	83.827

Table 24 outlines those costs for which no information was available about the distribution and therefore utilised a uniform.

Table 24 PSA uniform distribution of costs

		Mean	Lower	Upper
Ablation capital costs	PDT	9234.299	0.000	10000.000
	RFA	4617.150	0.000	10000.000
	APC	1539.050	0.000	10000.000
Excess days		3.310	0.000	5.000
RFA consumable		2000	0	2000
Photosensitive drugs		2409.000	1540.000	2409.000
Chemotherapy proportion		0.560	0.000	1.000
Purchase Price - PDT		60000.000	0.000	120000.000
Purchase Price - APC		10000.000	0.000	20000.000
Purchase Price - RFA		30000.000	0.000	60000.000
Life span of technologies		7.500	5.000	10.000
Resale value		0.000	0.000	0.000
Annuity factor		6.498		

9.4 Structural sensitivity analysis

The following structural assumptions and variables will be explored in sensitivity analysis:

- Age dependent utilities

Presently the model assumes age independent utilities this ignores potential changes in peoples quality of life over time. So age dependent utilities will be included and the current base estimates in the model as multipliers.

- Time horizon

The time horizon will be altered from 10, 20 and 50 years

- Age of the cohort

The base case assumes an average age of 60 years for the cohort. Other cost effectiveness analyses use 50 years as this is apparently the average of diagnosis in the US. Average ages of 50, 55, 60 and 65 will be explored.

- Removing retreatment

Treatment is often dependent on whether a patient is able to tolerate treatment therefore will be removed after 80 years of age.

- Surveillance

It will be examined what occurs when treatment is not followed up by surveillance to explore the worst possible example of poor follow-up. The effect of stopping surveillance at various time points will also be explored.

9.5 Scenario analysis

- Non specialist centre's

All the trials and studies were conducted in specialist centres and under experienced clinicians. An issue for guidance production is what happens if these procedures are conducted in non-specialist centres. The GDG considered that potential results could be higher mortality from surgery, higher rates of perforation, lower effectiveness.

- Treatment effects

To explore the uncertainty around the estimates of efficacy for EMR and ablation. Their associated uncertainty will be increased by increasing the priors. This will have the effect of reducing the effectiveness of the treatments.

9.6 Expected value of information

Value of information analysis is used to identify the parameters which contribute most to decision uncertainty. Decision uncertainty can be defined as the probability that a wrong decision concerning optimal therapy is made and the consequences of such a wrong decision. Value of information analysis is conducted for all parameters within the model and for different subsets of parameters. Decision uncertainty can be measured in terms of opportunity loss – the probability that a wrong decision is made multiplied by the consequence of these wrong decisions. Value of information analysis can identify the reduction in opportunity loss associated with having perfect information about a parameter or group of parameters. By having perfect information we necessarily will have less uncertainty and thus less opportunity loss.

Expected value of perfect information (EVPI) is the estimate of opportunity loss for all parameters. Expected value of perfect parameter (EVPPI)

information is the opportunity loss associated with imperfect information on specific parameters. EVPI and EVPPI will be conducted to identify whether further research is required and in what areas. For EVPI the approximate size of the population is required. Therefore, based on estimates from Garside et al 2006 the estimated size of the population in England and Wales is approximately 500. This is assuming a population of 54.4 million, 1.25% with upper gastrointestinal problems and 1.75% are diagnosed with Barrett's and then 4% have HGD.

10 Results

10.1 Validation

Mortality

Below in figure 4 is a survival graph from the model for each of the treatment options:

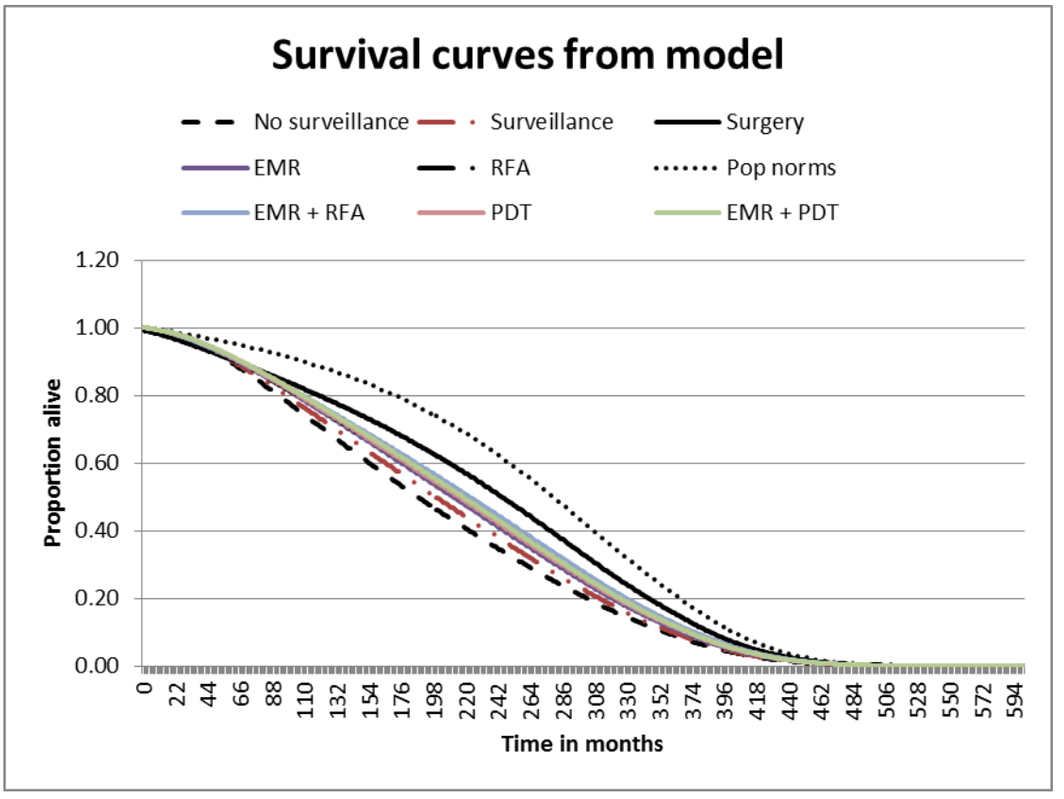

Figure 4 Model derived survival curves

Table 25 outlines the de novo cancer (minus recurrent cancer) incidence over the 50 year time horizon plus 5 year survival.

Table 25 5 year cancer incidence and survival from model

Treatment	Cancer incidence	5 year survival
No surveillance	5.77%	90%
Surveillance	5.79%	90%
Surgery	0.95%	91%
EMR	4.38%	91%
RFA	4.27%	91%
PDT	4.49%	91%
EMR plus RFA	3.53%	91%
EMR plus PDT	4.01%	92%
EMR plus APC	3.85%	91%

The 5 year survival figures for surgery are consistent with evidence from Prasad et al 2009 (95% overall survival at 5 years). The other estimates for endotherapies and no active treatment are generally higher than the estimates from the identified clinical studies (please see GRADE tables in section 13.5 for more details) which have estimates that vary from 81% to 91%. However, the studies were generally of low quality and therefore, it is difficult to derive firm conclusions. The incidences of cancer for no surveillance and surveillance are in line with the inputted probabilities. This is reasonable because these treatments do not prevent cancer but ensure they are treated early. For surgery the estimates from Prasad et al 2008 and 2009 indicated a rate of between 0.56% and 1.5% so the reported value of 0.95% appears reasonable. For the ablation treatments the model predicts a reduction in cancer progression of between 39% and 23%. Evidence from Shaheen et al 2009 estimates a reduction of 90% and from Overholt et al 2005:2007 estimates a reduction of 47%. These results suggest that cancer incidence has not been reduced as significantly as the trials suggest. This could be because the natural history has not been altered to account for the effect of treatment. This is a limitation that will be considered when assessing the results.

10.2 Deterministic results and sensitivity analysis

10.2.1 Breakdown of costs and QALYs

Full breakdown of costs and QALYs are presented in section 13.11. The breakdown of the QALYs indicates that the post surgery well states contribution is very important in determining cost effectiveness otherwise no surveillance would dominate them. From the breakdown of the costs the biggest drivers appear to be surveillance and treatment costs.

10.2.2 Table of results

Table 26 presents the deterministic base case results from the analysis. From this analysis surgery, EMR, EMR plus RFA, EMR plus APC and EMR plus PDT can all be considered cost effective with ICERs below £20,000 per QALY

gained. RFA and PDT alone are associated with more uncertainty around concluding they are cost effective with ICERs between £20,000 and £30,000 per QALY gained. In this analysis surveillance is not considered cost effective. These results are in line with the clinical and cost inputs since EMR plus RFA and APC are the most effective at ablating dysplasia and are relatively cheaper than the alternatives.

Table 26 Deterministic base case results

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.89	8782	0.00	0	-
Surveillance	8.27	22233	0.38	13450	35277
Surgery	9.18	15971	1.29	7189	5560
EMR + surveillance	8.73	20464	0.84	11682	13846
RFA + surveillance	8.92	34522	1.04	25740	24829
PDT + surveillance	8.87	31480	0.99	22698	23002
EMR + RFA + surveillance	9.23	27644	1.35	18862	13990
EMR + PDT + surveillance	9.18	31233	1.30	22451	17327
EMR + APC + surveillance	9.13	24047	1.24	15265	12300

10.3 Deterministic sensitivity analysis

10.3.1 Transition matrices

Table 27 presents the results if the upper estimates are used.

Table 27 Deterministic results with upper estimates for transitions

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.91	9095	0.00	0	-
Surveillance	8.32	18211	0.40	9116	22756
Surgery	9.18	15971	1.26	6876	5438
EMR + surveillance	9.47	15142	1.56	6047	3886
RFA + surveillance	10.16	29174	2.24	20079	8947
PDT + surveillance	9.95	26346	2.04	17251	8470
EMR + RFA + surveillance	10.69	21765	2.77	12670	4573
EMR + PDT + surveillance	10.75	24835	2.83	15740	5558
EMR + APC + surveillance	10.52	17928	2.61	8833	3390

And table 28 presents the results when the lower estimates are used

Table 28 Deterministic results with lower estimates for transitions

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	8.71	7574	0.00	0	-
Surveillance	8.92	23089	0.21	15516	72302
Surgery	9.18	15971	0.47	8397	17845
EMR + surveillance	9.11	21309	0.40	13735	33937
RFA + surveillance	9.36	35371	0.65	27797	42789
PDT + surveillance	9.33	32355	0.62	24781	40215
EMR + RFA + surveillance	9.58	28361	0.87	20787	23771
EMR + PDT + surveillance	9.59	32030	0.88	24456	27787
EMR + APC + surveillance	9.50	24804	0.79	17230	21710

As can be seen the natural history transitions have a significant impact on the estimates of cost effectiveness. We will assess the importance of other transitions in deterministic sensitivity analysis. However, it would appear that the more aggressive the condition is active interventions appear more cost effective.

10.3.2 One to one sensitivity analysis

Section 13.10 outlines the one-to-one sensitivity analyses conducted. These results indicate that the results are robust within the ranges specified. The major parameters that appear to affect the cost effectiveness estimate the most are the cost of pathology and endoscopy and the probability of transiting to cancer after surgery for early cancer. These factors make intuitive sense since pathology and endoscopy are essential for surveillance which is a major contributor to the total costs for the ablative therapies as demonstrated by the breakdown of the costs. In addition, if the probability of relapsing early after surgery is high it reduces the benefit of early intervention and therefore surveillance becomes less cost effective.

10.3.3 Age of the cohort

Table 29 presents the mean deterministic ICER for each of the treatments for various average ages for the cohort.

Table 29 ICERs for each treatment at various ages assumed for the cohort

Age	50	55	60	65
Surveillance	£29351	£31738	£35277	£40583
Surgery	£4096	£4667	£5560	£7005
EMR + surveillance	£11596	£12531	£13846	£15689
RFA + surveillance	£19623	£21772	£24829	£29234
PDT + surveillance	£18327	£20256	£23002	£26961
EMR + RFA + surveillance	£11082	£12285	£13990	£16434
EMR + PDT + surveillance	£13700	£15198	£17327	£20395
EMR + APC + surveillance	£9883	£10885	£12300	£14319

These results indicate that the younger the cohort the more improved the costs effective results. This is an important consideration when examining other published cost effectiveness analyses since the majority examines a cohort of 50 years.

10.3.4 Quality of life estimates

Table 30 presents the results if it is assumed that quality of life is based on the diagnostic categorisation of the patient instead of their health state.

Table 30 Deterministic results with quality of life linked to diagnosis

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.07	8782	0.00	0	-
Surveillance	8.04	22233	0.97	13450	13851
Surgery	8.90	15971	1.83	7189	3931
EMR + surveillance	8.50	20464	1.43	11682	8181
RFA + surveillance	8.68	34522	1.61	25740	16007
PDT + surveillance	8.63	31480	1.56	22698	14552
EMR + RFA + surveillance	8.98	27644	1.91	18862	9871
EMR + PDT + surveillance	8.93	31233	1.86	22451	12084
EMR + APC + surveillance	8.88	24047	1.81	15265	8447

As can be seen this greatly improves the estimates of cost effectiveness and suggests that if the quality of life is strongly linked to diagnosis rather than the underlying health state then there is the possibility that surveillance and therefore all treatments may be more cost effective than the base case analysis indicates.

If weighting is removed and just the unaltered numbers from Gerson et al 2006 are utilised the results in table 31 are produced. As can be observed all the estimates improve from the base case. This is because without the general population weighting the potential benefit is increased be person and therefore more QALYs are available.

Table 31 Deterministic results with no population quality of life weighting

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	9.88	8782	0.00	0	-
Surveillance	10.35	22233	0.47	13450	28350
Surgery	11.49	15971	1.61	7189	4465
EMR + surveillance	10.91	20464	1.04	11682	11277
RFA + surveillance	11.16	34522	1.28	25740	20132
PDT + surveillance	11.10	31480	1.22	22698	18656
EMR + RFA + surveillance	11.55	27644	1.67	18862	11299
EMR + PDT + surveillance	11.48	31233	1.60	22451	14000
EMR + APC + surveillance	11.41	24047	1.53	15265	9945

10.3.5 Age dependant utilities

Making the utilities age dependant deterministic cost effectiveness results are presented in table 32 and the probabilistic results are presented in table 36.

Table 32 Deterministic results using age dependant utilities

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.68	8782	0.00	0	-
Surveillance	8.04	22233	0.36	13450	37003
Surgery	8.90	15971	1.23	7189	5869
EMR + surveillance	8.49	20464	0.81	11682	14461
RFA + surveillance	8.67	34522	0.99	25740	25968
PDT + surveillance	8.62	31480	0.94	22698	24063
EMR + RFA + surveillance	8.97	27644	1.29	18862	14623
EMR + PDT + surveillance	8.92	31233	1.24	22451	18120
EMR + APC + surveillance	8.86	24047	1.19	15265	12858

These results indicate that age dependant utilities result in the ICERs increasing. This is probably due to the potential benefit from treatment being reduced as demonstrated by the reduced QALY from no surveillance.

However, this is unlikely to be a valid analysis since various quality of life data is being mixed together and adding additional data when it is already inconsistent does not appear to be advised.

10.3.6 Zero capital costs

Table 33 presents results if zero capital costs are assumed. As can be seen the cost effectiveness of the ablative therapies improve across all the technologies, bringing the ICERs closer to £20,000 per QALY. This therefore supports the use of these technologies in centres where capital costs can be reduced for example by leasing equipment.

Table 33 Deterministic results with zero capital costs

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.89	8782	0.00	0	-
Surveillance	8.27	22233	0.38	13450	35277
Surgery	9.18	15971	1.29	7189	5560
EMR + surveillance	8.73	20464	0.84	11682	13846
RFA + surveillance	8.92	31564	1.04	22782	21976
PDT + surveillance	8.87	28926	0.99	20144	20414
EMR + RFA + surveillance	9.23	25964	1.35	17181	12744
EMR + PDT + surveillance	9.18	28704	1.30	19922	15376
EMR + APC + surveillance	9.13	23623	1.24	14841	11959

10.4 Probabilistic sensitivity analysis

10.4.1 Table of results

Table 34 presents the results of the probability sensitivity analysis. The QALYs increase for all treatments, but most for no surveillance which subsequently reduces the incremental differences in health benefit. The costs also increase, but for no surveillance they increase the least subsequently increasing the incremental cost. This therefore, causes the cost effectiveness estimates to deteriorate. Only surgery, EMR plus RFA and EMR plus APC remain below £20,000 per QALY gained. This is probably linked to the higher

percentage rate of complete ablation of dysplasia in those treatments. EMR alone, RFA alone and EMR plus PDT are now between £20,000 and £30,000 per QALY gained. PDT alone is now over £30,000 per QALY gained and therefore conclusions on its cost effectiveness need significant consideration. Surveillance alone is now highly cost ineffective. This is the result of the costs increasing significantly and benefits decreasing significantly. From the deterministic sensitivity analysis this can be attributed to sensitivity in the natural history of the condition and the costs of surveillance.

Table 34 Probabilistic base case results

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	8.44	7249	0.00	0	-
Surveillance	8.50	22741	0.05	15491	283009
Surgery	9.25	15855	0.81	8606	10612
EMR + surveillance	8.98	20993	0.54	13743	25662
RFA + surveillance	9.15	24740	0.70	17490	24823
PDT + surveillance	9.09	32437	0.65	25188	38681
EMR + RFA + surveillance	9.44	23136	1.00	15887	15916
EMR + PDT + surveillance	9.38	32598	0.94	25348	26946
EMR + APC + surveillance	9.33	23924	0.89	16675	18745

10.4.2 Cost effectiveness plane

Figure 5 is the output of the probabilistic sensitivity analysis plotted on a graph of incremental costs and QALYs. From the graphs it appears that surgery is associated with considerable uncertainty in that the simulations are spread across the NW, NE and SE quadrants, so ranging from cost ineffective (NW) to cost saving (SE). The same is true for the other therapeutic options however, the spread is significantly less. The clouds for the ablative therapies and surveillance all follow a similar shape with little correlation between costs and effect. In particular there is a concentration of points along the y axis. The cost variation can be attributed to the cost of surveillance, something they all

share and surgery does not. It has little effect on preventing cancer therefore has a small effect on the health outcomes.

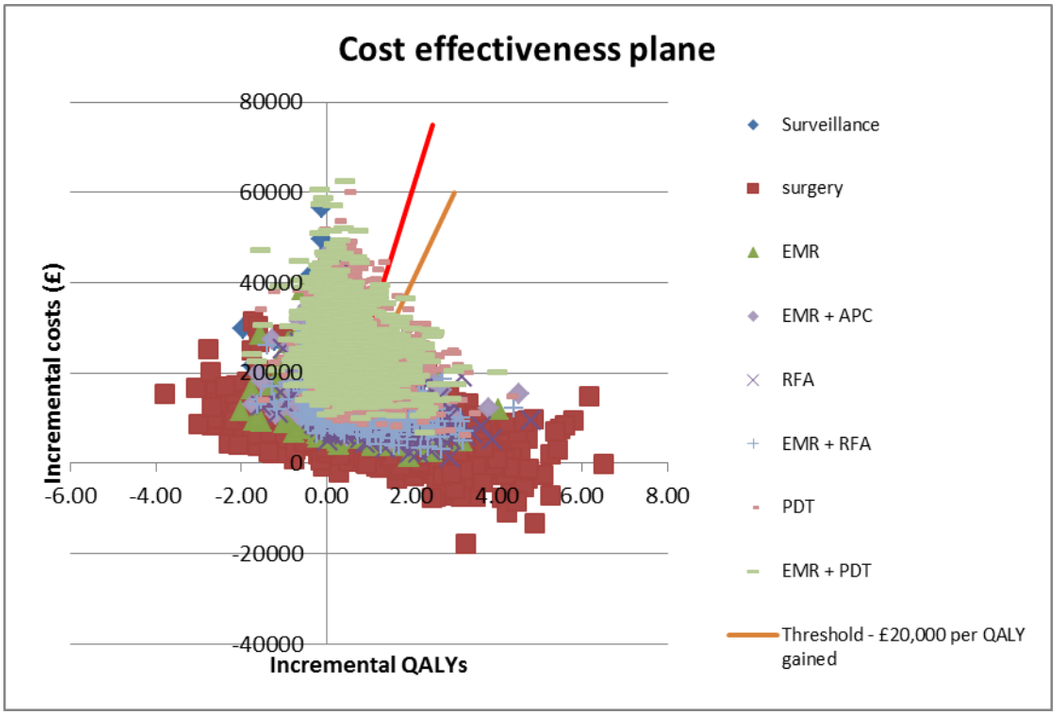

Figure 5 Cost effectiveness plane for all treatments

10.4.3 Cost effectiveness acceptability curves

Figure 6 presents the cost effectiveness acceptability curves for the therapeutic options.

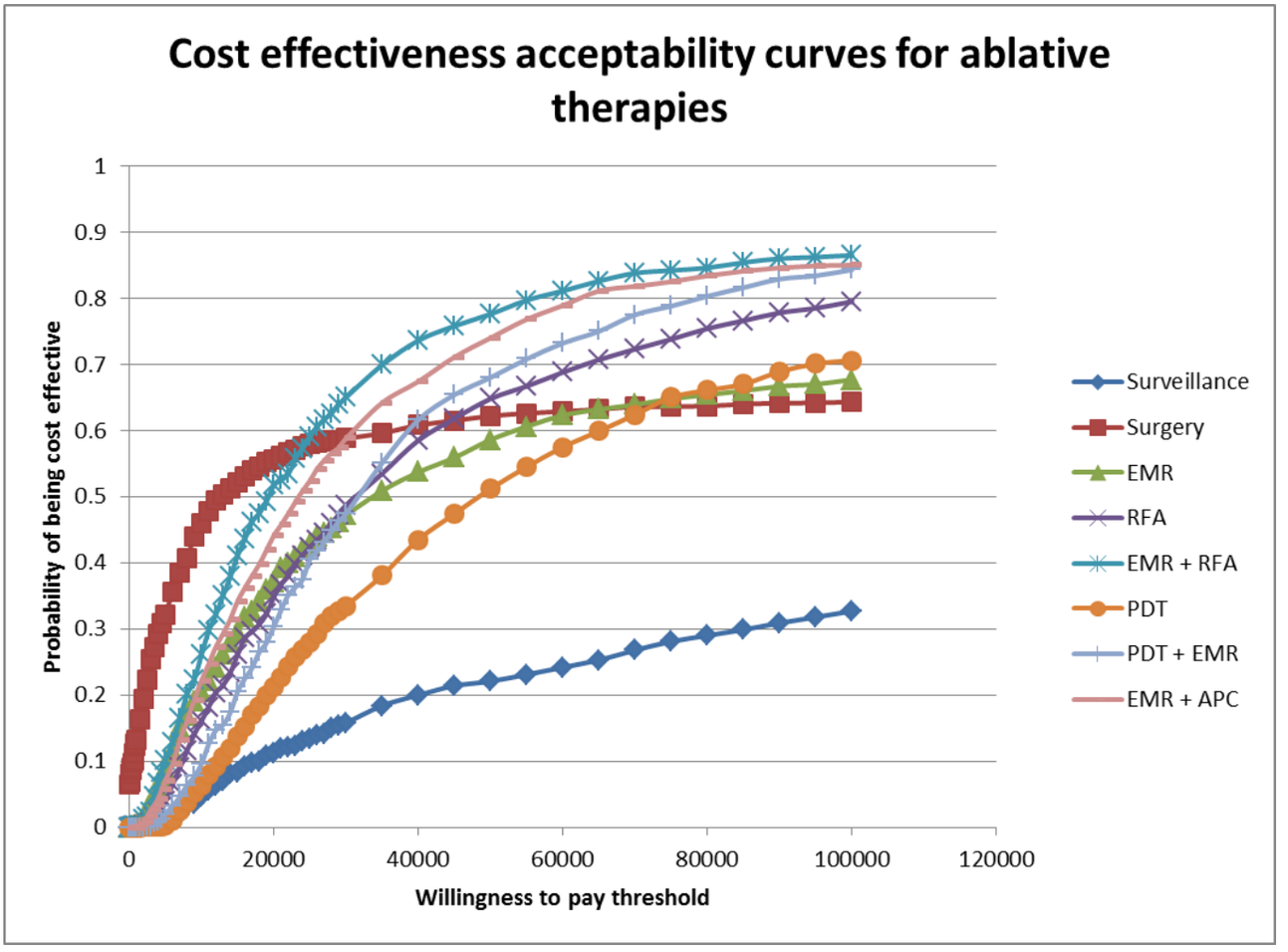

Figure 6 Cost effectiveness acceptability curves for all treatments

Table 35 shows the probability of being cost effectiveness at a WTP threshold of £20,000 and £30,000 per QALY gained.

Table 35 Probability of treatments being cost effective at £20,000 and £30,000 willingness to pay thresholds

Treatment	Prob. of being cost effective	
	£20,000	£30,000
Surveillance	0.108	0.168
Surgery	0.575	0.617
EMR	0.355	0.444
RFA	0.390	0.534
PDT	0.201	0.333
EMR plus RFA	0.554	0.700
EMR plus PDT	0.307	0.480
EMR plus APC	0.451	0.604

At £20,000 per QALY gained the surgery has the highest probability of being cost effective, this is followed by EMR plus RFA. The other options all have a less than 50% chance of being cost effective. At a £30,000 per QALY threshold EMR plus RFA swaps places with surgery as the most likely to be cost effective. The only options that remain lower than 50% are EMR, PDT and surveillance alone. The probability of surgery being cost effective levels off at 65% indicating that approximately 45% of the points on the cost effectiveness plane are in the North West quadrant. For the other treatments it is apparent that a far smaller proportion of the simulations lie in the North West quadrant.

10.4.4 Cost effectiveness acceptability frontiers

Figure 7 presents the cost effectiveness acceptability frontier of the ablative therapies.

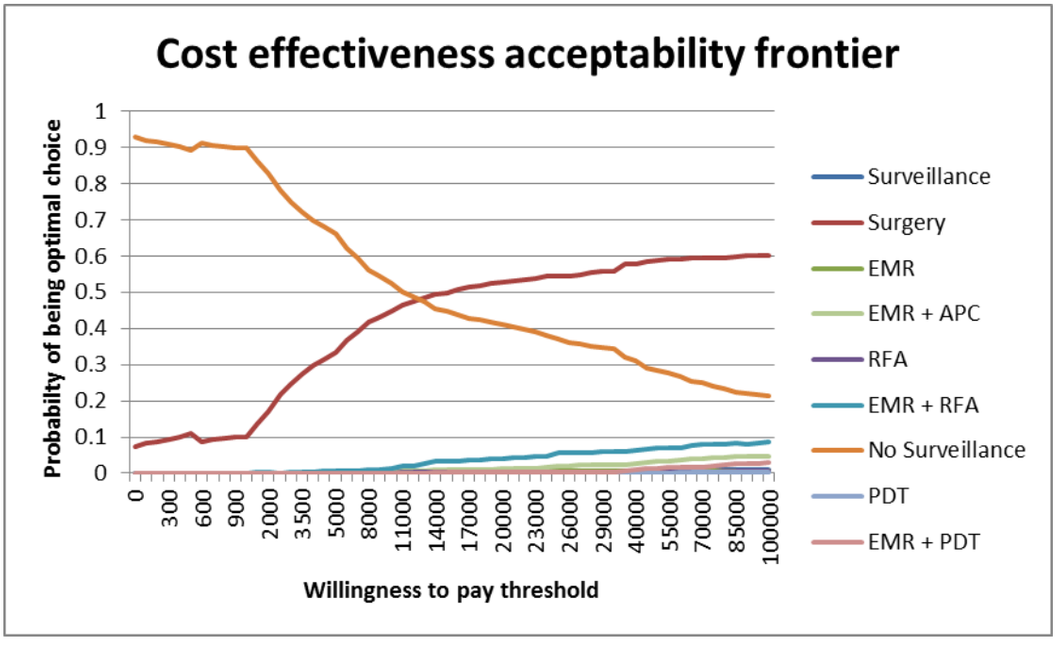

Figure 7 Cost effectiveness acceptability frontier

Table 36 presents the probability of being the optimal choice at a WTP of £30,000 per QALY gained.

Table 36 Probability of treatment being the optimal choice at £20,000 and £30,000 willing to pay thresholds

Treatment	Probability of being optimal choice	
WTP	£20,000	£30,000
No surveillance	0.300	0.192
Surveillance	0.000	0.000
Surgery	0.498	0.501
EMR	0.017	0.017
RFA	0.008	0.012
PDT	0.000	0.002
EMR plus RFA	0.135	0.201
EMR plus PDT	0.005	0.014
EMR plus APC	0.037	0.061

The model predicts that the optimal choice in most situations is surgery with a probability over 50% at both thresholds. No surveillance is the second most likely to be the optimum choice followed by EMR plus RFA. The other options have a very low probability of ever being cost effective. These results suggest that in situations that result in good cost effectiveness estimates for the ablation therapies surgery is more dominant. This could be attributed to the fact that surgery is the cheapest option, due to the lack of surveillance However, given the very poor quality of the underlying estimates of effectiveness and the lack of comparative data it is inappropriate to draw conclusions from this analysis.

10.5 Structural sensitivity analysis

10.5.1 Time horizon

Tables 37, 38 and 39 are the corresponding deterministic cost effectiveness results at 10, 20 and 50 years

Table 37 Deterministic results at 10 years

10 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	4.43	4677	0.00	0	-
Surveillance	5.06	16034	0.63	11357	17996
Surgery	5.28	12027	0.86	7350	8586
EMR + surveillance	5.26	14626	0.84	9949	11858
RFA + surveillance	5.33	28403	0.90	23726	26321
PDT + surveillance	5.30	25329	0.88	20651	23530
EMR + RFA + surveillance	5.46	22108	1.03	17430	16847
EMR + PDT + surveillance	5.43	25352	1.00	20675	20608
EMR + APC + surveillance	5.41	18456	0.99	13778	13938

Table 38 Deterministic results at 20 year

20 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.14	7938	0.00	0	-
Surveillance	7.44	20875	0.30	12937	42942
Surgery	8.05	14818	0.91	6879	7580
EMR + surveillance	7.81	19095	0.67	11157	16620
RFA + surveillance	7.95	33075	0.81	25137	31000
PDT + surveillance	7.92	30036	0.77	22098	28581
EMR + RFA + surveillance	8.20	26282	1.05	18344	17422
EMR + PDT + surveillance	8.16	29807	1.01	21869	21605
EMR + APC + surveillance	8.11	22692	0.97	14754	15192

Table 39 Deterministic results at 50 year

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.89	8782	0.00	0	-
Surveillance	8.27	22233	0.38	13450	35277
Surgery	9.18	15971	1.29	7189	5560
EMR + surveillance	8.73	20464	0.84	11682	13846
RFA + surveillance	8.92	34522	1.04	25740	24829
PDT + surveillance	8.87	31480	0.99	22698	23002
EMR + RFA + surveillance	9.23	27644	1.35	18862	13990
EMR + PDT + surveillance	9.18	31233	1.30	22451	17327
EMR + APC + surveillance	9.13	24047	1.24	15265	12300

These results indicate that surveillance is cost effective in the short run but becomes less cost effective as the time horizon is increased. This indicates that a surveillance strategy focus on those at highest risk of cancer. Potentially biological factors would be required. For all the other active treatments the longer time horizon allows for a greater accumulation of QALYs with a relatively lower accumulation of costs thereby improving the cost effectiveness estimates

10.5.2 Removing retreatment

Table 40 presents the results of removing the option of retreatment and surveillance after people are 80 years old or over. This has a very minor effect on the cost effectiveness estimates for the ablative therapies. However, they do improve suggesting that our baseline figures could potentially overestimate the cost effectiveness estimates since the number of treatments received would be dependent on the person's state of health.

Table 40 Deterministic base case results with no retreatment or surveillance after 80 years

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.89	8782	0.00	0	-
Surveillance	8.26	21759	0.37	12976	34608
Surgery	9.18	15971	1.29	7189	5560
EMR + surveillance	8.72	19974	0.83	11192	13425
RFA + surveillance	8.91	33890	1.03	25108	24440
PDT + surveillance	8.86	30871	0.98	22089	22601
EMR + RFA + surveillance	9.22	27083	1.34	18301	13677
EMR + PDT + surveillance	9.17	30620	1.29	21838	16989
EMR + APC + surveillance	9.12	23519	1.23	14737	11973

10.5.3 Surveillance

Table 41 presents results assuming no surveillance after treatment. It demonstrates that continued surveillance is not essential for the ablative therapies to be considered cost effective. However, the incremental health benefits are reduced therefore, suggesting that surveillance may be necessary to achieve the highest health gain.

Table 41 Deterministic base case results with no surveillance after treatment

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.89	8782	0.00	0	-
Surveillance	8.26	21759	0.37	12976	34608
Surgery	9.18	15971	1.29	7189	5560
EMR + surveillance	8.38	9400	0.49	617	1261
RFA + surveillance	8.59	21983	0.70	13200	18864
PDT + surveillance	8.52	18815	0.64	10033	15796
EMR + RFA + surveillance	8.93	16856	1.04	8074	7751
EMR + PDT + surveillance	8.85	19283	0.96	10501	10927
EMR + APC + surveillance	8.80	13068	0.91	4285	4692

The probabilistic results are presented in table 42.

Table 42 Probabilistic base case results with no surveillance after treatment

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	8.41	7327	0.00	0	-
Surveillance	8.49	22528	0.08	15202	191605
Surgery	9.32	15834	0.91	8507	9342
EMR + surveillance	8.86	9814	0.45	2488	5502
RFA + surveillance	9.04	13000	0.64	5674	8921
PDT + surveillance	8.99	19970	0.58	12643	21760
EMR + RFA + surveillance	9.34	12624	0.93	5297	5702
EMR + PDT + surveillance	9.28	20463	0.87	13136	15014
EMR + APC + surveillance	9.23	12805	0.82	5478	6680

These results indicate that it is surveillance that is driving the uncertainty in the estimates of cost effectiveness for the ablative therapies, especially for PDT. This is discussed in greater detail in section 11.

10.5.4 Quality of life estimates

Table 43 outlines the quality of life estimates if it is assumed that Barrett's oesophagus is not associated with decreasing quality of life as the condition progresses. These cause the ICERs to increase considerably. This suggests that the assumptions surrounding quality of life are very important to the assessment of cost effectiveness.

Table 43 Deterministic results assuming quality of life not associated with Barrett's progression

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.93	8782	0.00	0	-
Surveillance	8.26	22233	0.32	13450	41806
Surgery	9.18	15971	1.25	7189	5762
EMR + surveillance	8.51	20464	0.58	11682	20279
RFA + surveillance	8.83	34522	0.90	25740	28633
PDT + surveillance	8.77	31480	0.83	22698	27226
EMR + RFA + surveillance	9.13	27644	1.20	18862	15756
EMR + PDT + surveillance	9.09	31233	1.16	22451	19427
EMR + APC + surveillance	9.01	24047	1.07	15265	14234

10.6 Scenario sensitivity analysis

10.6.1 Priors

In the following analyses it will be explored what happens if just the transitions from Garside et al 2006 are used. In this case the priors are set to uninformative and therefore increase the relative importance of the transitions from Garside et al 2006. In addition, for the recurrence of cancer post surgery for HGD the estimate from Garside will be used instead of from Prasad et al 2008, 2009. Table 44 outlines the deterministic results. These demonstrate that just using the estimates from Garside et al 2006 results in none of the estimates being cost effective. If the estimate of recurrence from Prasad is used it reduces the ICER of surgery to £36,684.

Table 44 Deterministic results assuming Garside et al 2006 transitions

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.50	8572	0.00	0	-
Surveillance	7.81	25554	0.31	16982	54903
Surgery	4.72	21156	-2.78	12584	-4528
EMR + surveillance	7.89	25786	0.39	17214	44421
RFA + surveillance	7.89	39427	0.39	30855	79932
PDT + surveillance	7.92	36216	0.42	27644	65358
EMR + RFA + surveillance	7.85	34074	0.35	25502	72413
EMR + PDT + surveillance	7.94	37044	0.44	28472	64582
EMR + APC + surveillance	7.89	30151	0.39	21579	55262

These results indicate that the assumption of non step wise progression made by the GDG results in the treatments becoming cost effective. However, the results indicate that the probability of regressing to non-dysplastic Barrett's or no Barrett's oesophagus falls to 0.3% which is far lower than the placebo arms in Overholt et al 2005:2007 or Shaheen et al 2009. With the base case this rises to 5.6% which is still lower but is more in line than the Garside et al 2006 estimates.

10.6.2 Non-specialist centres

To represent non-specialist centres the probability of perforations is increased and reduced the potential effectiveness of EMR. This was a specific concern expressed by the GDG. Therefore, the risk of a perforation was raised to 10% and the effectiveness estimates of the ablative therapies were reduced by 10%.

Table 45 presents the deterministic results; table 46 presents the probabilistic results.

Table 45 Deterministic results for non-specialist centres

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.89	8782	0.00	0	-
Surveillance	8.27	22233	0.38	13450	35277
Surgery	9.18	15971	1.29	7189	5560
EMR + surveillance	8.30	20905	0.42	12123	29073
RFA + surveillance	8.47	34830	0.58	26048	44569
PDT + surveillance	8.43	31751	0.55	22969	42076
EMR + RFA + surveillance	8.72	28278	0.83	19496	23380
EMR + PDT + surveillance	8.69	31714	0.80	22931	28642
EMR + APC + surveillance	8.63	24616	0.75	15833	21156

Table 46 Probabilistic results for non-specialist centres

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	8.18	7239	0.00	0	-
Surveillance	8.21	22488	0.04	15248	429188
Surgery	9.01	15763	0.83	8523	10257
EMR + surveillance	8.28	21375	0.10	14136	144807
RFA + surveillance	8.41	22946	0.23	15707	67365
PDT + surveillance	8.38	32730	0.20	25491	126018
EMR + RFA + surveillance	8.64	22084	0.46	14845	32438
EMR + PDT + surveillance	8.61	32926	0.43	25686	60051
EMR + APC + surveillance	8.57	24336	0.39	17096	43454

These results indicate that to achieve the estimates of cost effectiveness in the base case, these treatments should be restricted to specialist centres otherwise the cost effectiveness results will be severely affected.

10.6.3 Treatment effectiveness

All the estimates of effectiveness are associated with uncertainty, since they were based on non-randomised non-comparative studies apart from RFA and

PDT. Therefore, the priors will be altered to make the estimates of relative effectiveness more uncertain by adopting as our prior belief that these treatments have no effect on the percentage achieving complete ablation of dysplasia. The deterministic results are presented in table 47 and the probabilistic results are presented in table 48.

Table 47 Deterministic results after increasing uncertainty around results

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	7.68	8782	0.00	0	-
Surveillance	8.04	22233	0.36	13450	37003
Surgery	8.90	15971	1.23	7189	5869
EMR + surveillance	8.21	21483	0.54	12701	23654
RFA + surveillance	8.67	34522	0.99	25740	25968
PDT + surveillance	8.62	31480	0.94	22698	24063
EMR + RFA + surveillance	8.46	29416	0.78	20634	26355
EMR + PDT + surveillance	8.43	32642	0.76	23860	31531
EMR + APC + surveillance	8.41	25542	0.73	16759	22973

Table 48 Probabilistic results after increasing uncertainty around results

50 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
No surveillance	8.08	7491	0.00	0	-
Surveillance	8.16	22246	0.07	14756	199448
Surgery	9.00	15582	0.92	8091	8818
EMR + surveillance	8.36	21936	0.27	14445	53004
RFA + surveillance	8.79	22367	0.71	14876	20969
PDT + surveillance	8.75	32336	0.66	24846	37529
EMR + RFA + surveillance	8.58	23032	0.50	15541	31118
EMR + PDT + surveillance	8.56	33655	0.47	26164	55275
EMR + APC + surveillance	8.54	25091	0.45	17600	38754

These results indicate that the cost effectiveness estimates are highly sensitive to changes in the clinical effectiveness estimates, suggesting this could be an area of important investment.

10.7 Value of information analysis

10.7.1 EVPI and population EVPI

The value of information analysis calculated that the value of additional research per person at £30,000 per QALY WTP is £16,525. The population EVPI i.e. for the population of patients who could potentially benefit from the treatment is £61,424,686. A graph of per person EVPI for various WTP thresholds is presented in figure 8. This indicated that at approximately £30,000 per QALY our willingness to pay for extra research increase exponentially. If this value is greater than the cost of conducting the research then it is valuable.

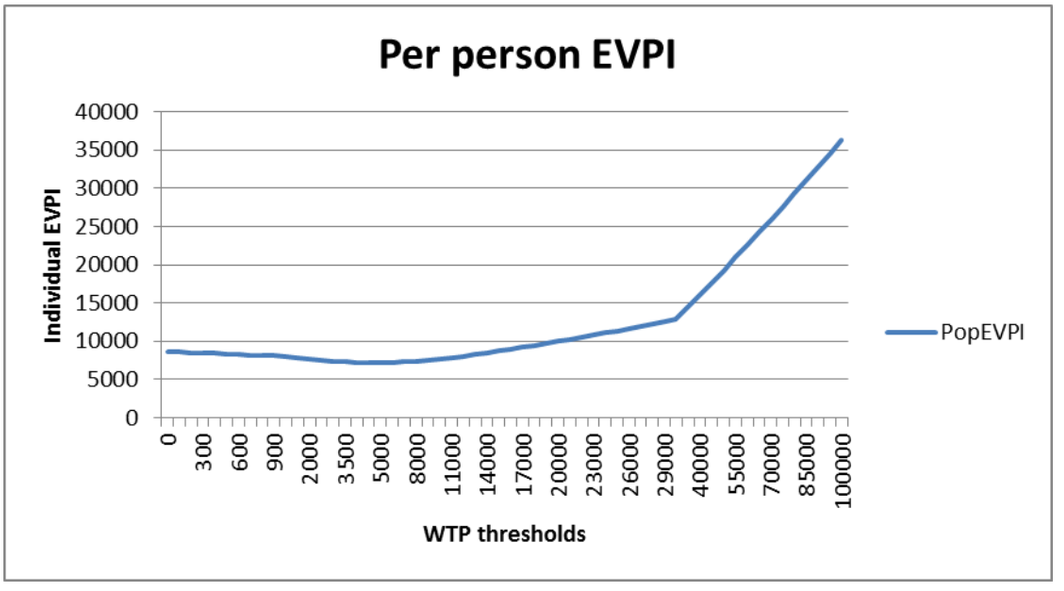

Figure 8 Per person expected value of perfect information

10.7.2 Expected value of perfect parameter information

Figure 9 presents the results of the expected value of perfect parameter information (EVPPI) analysis and indicate that the most important parameter

to conduct further research into is natural history the WTP threshold used was £30,000 per QALY.

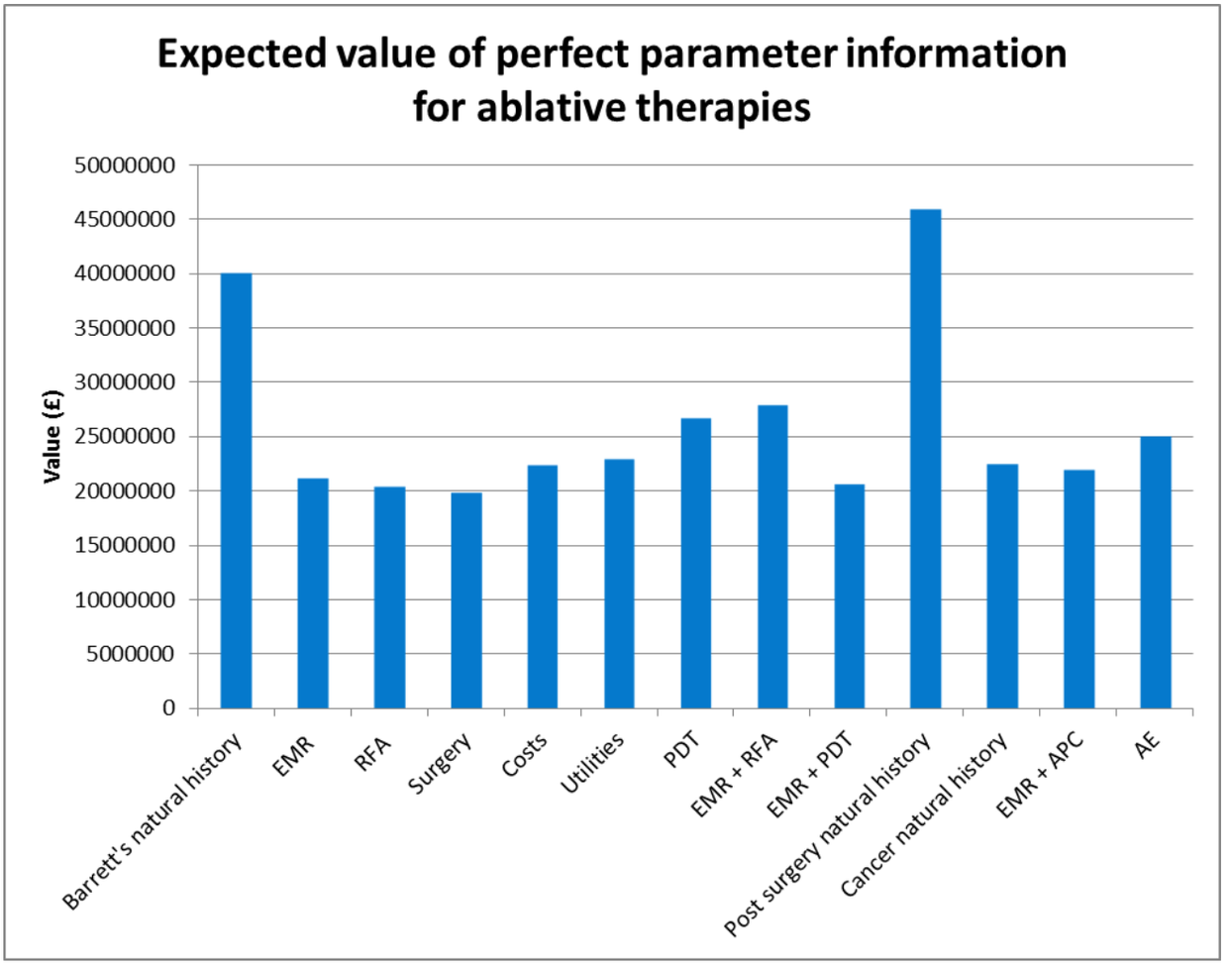

Figure 9 Expected value of perfect parameter information for ablative therapies

These results indicate that all areas of the analysis could use research, which is consistent with the evidence from the cost effectiveness planes. The results do indicate that the entire natural history of Barrett's should be a priority for research. This is intuitive as can be seen from the difference between a step-wise progression and more volatile transitions (see section 10.3.1 and 10.6.1). In addition, if all the ablative therapies as a group the combined value of trials to evaluate their relative effectiveness would resolve a large proportion of the uncertainty inherent in the model.

11 Discussions and conclusions

11.1 *Discussions*

In section 13.13 is a quality checklist for new cost effectiveness analysis. It appears that the analysis is based on robust methodology and has been clearly outlined. In addition, the majority of areas where uncertainty exists have been explored through numerous analyses.

11.1.1 Surveillance cost effectiveness results

There is a major discrepancy between the deterministic and probabilistic results for surveillance alone which deserves further explanation. The PSA results are presented below in figure 10.

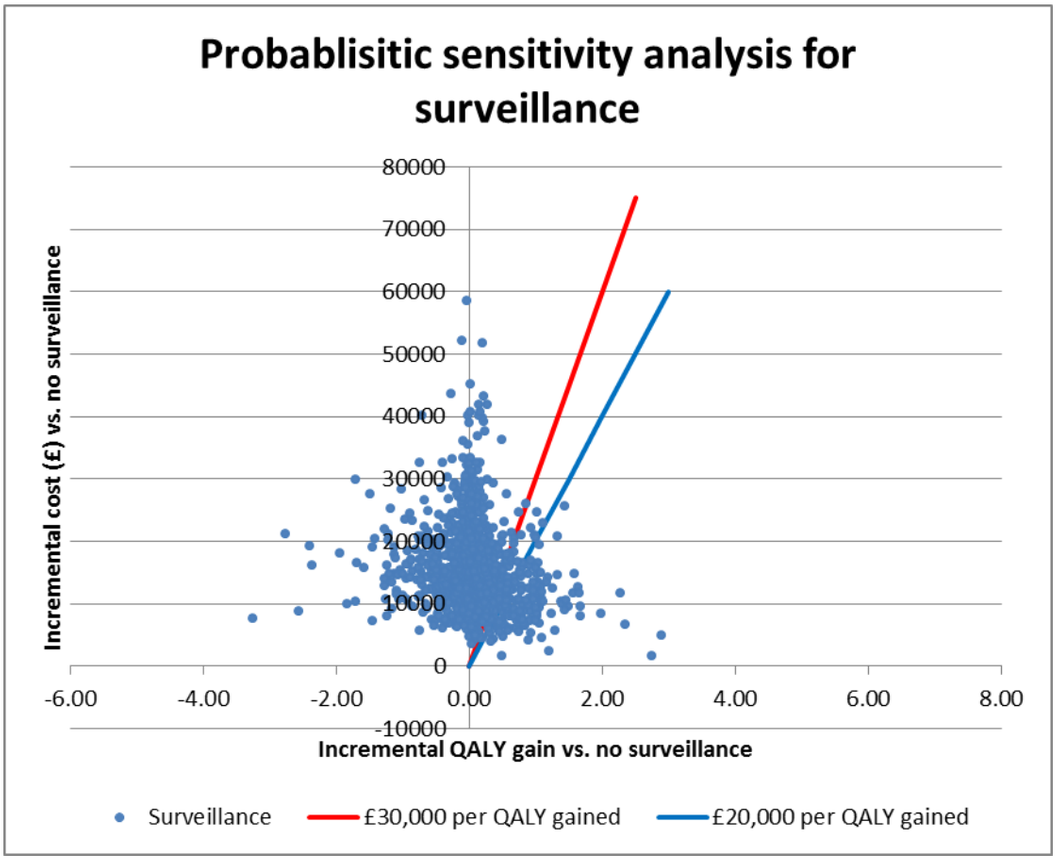

Figure 10 Cost effectiveness plane for surveillance

The plot demonstrates that the simulations are clustered around the y-axis this means there are a number of simulations with negative benefits. These

negative results produce an average incremental QALY close to zero. However, costs are higher for small benefits than they are for large positive and negative incremental QALYs. The result of these relationships is that the ICER calculation becomes very volatile as large costs are divided by small incremental benefits. Ergo the average ICER increases dramatically. The ICER is also very sensitive to changes in the parameters.

The impact of surveillance on the cost effectiveness of the endoscopic therapies is considerable as seen by analysis 10.5.5. Therefore, the main driver of the uncertainty is the value of surveillance post therapy. One issue that requires consideration is that the post cancer states represent a very simplified version of reality. Therefore, the benefit of surveillance may be underestimated.

Since this report and review focused on ablative therapy rather than surveillance this issue cannot be resolved here and further research and development is required. A more accurate modeling of oesophageal cancer may result in greater value in identifying cancer early and resulting greater health outcomes. However, it may also be possible that if Barrett's oesophagus is not as aggressive as presented in the base case then surveillance will be of little value as presented in analysis 10.3.1. Therefore, further research is also required on the natural history of Barrett's oesophagus and oesophageal cancer.

11.1.2 Strengths

The main strength of the analysis is its comprehensiveness by using the majority of the available data. It considers all the potential treatment options and uses the most up-to-date evidence available in the public domain.

The analyses attempts to consider the uncertainty in the data and therefore extensive sensitivity analysis have been conducted to explore it.

It has addressed a number of limitations with previous analyses by improving the modeling of post surgery, with the inclusion of different recurrence rates and also of attempting to model surveillance accurately.

11.1.3 Limitations

11.1.3.1 Clinical data

The clinical data was considered generally of poor quality with only two RCTs available and in both cases comparisons with placebo. Therefore comparative analysis between the treatments is not advised and also between surgery and ablative therapies is not recommended. In addition, their effect could have been underestimated as it was not possible to include a reduction in the probability of recurrence into the model to account for the lower progression to cancer seen in the clinical studies.

11.1.3.2 Natural history data post surgery

Unfortunately due to time constraints a new assessment of natural history for Barrett's oesophagus was not possible. Therefore, the HTA report by Garside et al 2006 was used. This means that there is the possibility that important new data has not been taken into account. In addition, this meant that the same assumptions as Garside et al 2006 were adopted concerning the combining of HGD and intramucosal cancer into one state and not incorporating sensitivity and specificity of endoscopic biopsy. These issues are particularly acute when considering post surgery and cancer which were very simplistic representations of reality. It is likely that if these states could be modeled more accurately with consideration of potentially different outcomes depending on when the cancer is detected, it would give a more accurate representation of surgery for cancer and post surgery survival. In addition, it would be better if chemoprevention could be modeled to take into account advances in cancer treatment and its associated costs. These issues also impact on the surveillance issues identified in section 11.1.1.

11.1.3.3 Systematic reviews

Ideally systematic reviews would have been carried out for all inputs into the model for the most robust evidence to be selected. However, the pragmatic approach adopted has the advantage that no data is likely to have been excluded and therefore represents a reasonable compromise.

11.1.3.4 Costing

The GDG highlighted that the NHS reference costs could potentially underestimate the true cost of the procedures. This was explored by increasing the costs in deterministic sensitivity analysis. It should be noted that the absolute costs are not the most important issue, but incremental costs. The use of the NHS tariff was considered, however the current version of the tariff does not differentiate between day cases and elective inpatients, which is an important factor in this analysis therefore it was not conducted. A true micro costing exercise in a UK setting would have been the preferred option.

11.1.3.5 Quality of life data

There remains uncertainty over the appropriate method to account for quality of life in Barrett's oesophagus. From the patient expert and clinical experts on the GDG the psychological burden of being diagnosed with Barrett's oesophagus and its grade can be very high as indicated by the work done by Gerson et al 2007b. It is not yet clear how the best way this should be accounted for in any analysis. The approach adopted in section 10.3.3 is one possibility; however more work is required in this area.

11.1.3.6 Treatment pathway

The current analysis simplifies the actual treatment administration by not accounting for the time required for multiple treatments. While the costs are accounted for it does not take into account the possibility of a person progressing between treatments, loss to follow up and so on. It is possible that this could further differentiate between the treatments and that if improved clinical effectiveness data is collected that this should be modeled in more detail in future to allow a true comparison to take place.

11.1.4 Conclusions

The current analysis indicates that surgery alone is the most cost effective therapy for Barrett's oesophagus. However, a large proportion of patients may

not be suitable and in addition given that it is a highly evasive treatment option suggests that patient choice in this instance is an important consideration. Evidence from the GDG indicates that patients are already looking for alternatives to surgery and that as long as ablative therapies are a cost effective that they should be considered as an alternative.

The current analysis indicates that EMR plus RFA and EMR plus APC are cost effective treatments with ICERs below £20,000 per QALY when deterministic and probabilistic analyses are considered. EMR alone, EMR plus PDT and RFA alone have cost effectiveness estimates that remain below £25,000 per QALY. PDT alone has cost effectiveness estimates that vary from £20,676 to £39,000 per QALY gained.

Given the poor quality of the data making comparisons and potentially ranking the treatments is unadvisable. Overall the ablative treatments appear cost effective. The exception is PDT; however, surveillance appears to be the main cause of the deteriorating probabilistic cost effectiveness results. As stated before it is likely that the fundamental structure of the model could have led to underestimating the benefit surveillance and ergo of the treatments. Therefore, it is likely that ablative treatments are a potentially cost effective treatment option.

However, any wide spread adoption should be treated with caution given the uncertainty in the analysis. These treatments should be confined to specialist centres to allow for the effectiveness seen in studies to be replicated in the NHS. In addition, it can allow for economies of scale since these treatments are very expensive for small centres.

11.1.5 Future work

There is an urgent need for work into the natural history of Barrett's oesophagus so that a true understanding of its course can be modeled. In addition future work into the clinical effectiveness of the ablative therapies especially compared to surgery is a priority.

Future models should attempt to consider the full course of the condition from diagnosis to post surgery to fully consider all the issues raised in this report. Therefore, the potential for discrete event simulation should be considered to make the modeling less time consuming.

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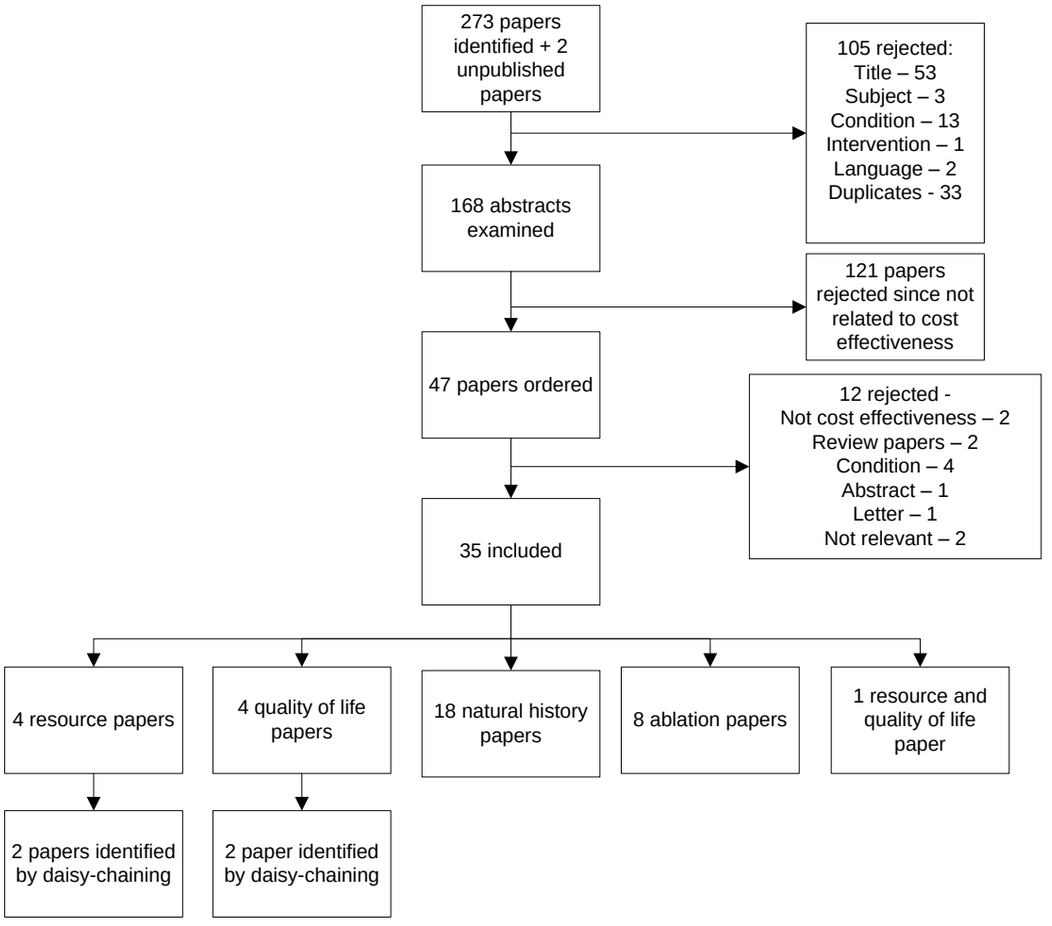
13 Appendices

13.1 Inclusion/exclusion



13.2 List of excluded papers

Study	Reason excluded
Dean et al 2001	Different condition
Harewood et al 2004	Cost comparison between conditions
Spechler et al 2004	Non systematic review
Pedrazzani et al 2005	Not cost effectiveness study
Canady et al 2006	Not cost effectiveness study
Provenzale et al 1990	Abstract
Inadomi et al 2007	Review article
Harris et al 1997	Different condition
Ofman et al 2000	Different condition
Gerson et al 2000	Different condition
Canto et al 2000	Article of different diagnosis techniques
Chin Hur 2005	Letter

13.3 Quality checklists – Ablation cost effectiveness studies

Full bibliographic reference	Das A, Wells C, Kim HJ et al. (2009) An economic analysis of endoscopic ablative therapy for management of nondysplastic Barrett's esophagus. Endoscopy 41(5):400-8
Source of funding	Unknown
Economic study type	Cost-effectiveness analysis conducted using a combined decision tree/Markov model.
Population, Country and perspective	50-year-old white mean recently diagnosed with non-dysplastic Barrett's oesophagus during endoscopy based on ACG definition. USA, payers perspective
Comparison(s)	Strategy 1 – Natural history (no surveillance) Strategy 2 – Endoscopic (surveillance) Strategy 3 – Ablate (HALO ablation system) (surveillance)
Source of effectiveness data	Based on published estimates – unknown if based on systematic review Utilities based on Provenzale et al 2009, Viji et al 2004 and Indomi et al 2003. Mortality from natural courses estimated from US life tables
Cost components	Based on US published data sources including Medicare/aid services and ambulatory payment classification and CPT. Additional costs were estimated.
Time horizon, discount rate	Life time for the cohort 3% cost discount. Unclear from text if discount applied to

	benefits
Results – cost	Per patient. Strategy 1 – $US 2894 Strategy 2 – $13016 Strategy 3 – $21919
Results – effectiveness	Per patient. Strategy 1 – 17.959 Strategy 2 – 18.076 Strategy 3 – 18.259
Results – adverse events	Number of oesophageal cancers (out 10000) Strategy 1 – 899 Strategy 2 – 518 Strategy 3 – 468
Results – Incremental cost-effectiveness	Strategy 1 – ref Strategy 2 – $86434 (vs. Strategy 1) Strategy 3 – $63416 (vs. Strategy 1) $48626 (vs. Strategy 2)
Results – Uncertainty	At willingness to pay threshold of under 60k strategy 1 is most cost effective. At thresholds greater than 60k strategy 3 is most cost effective.
Authors' conclusions	The authors conclude that for a 50 year old with NDBE ablation therapy yielded the highest QALY. They note that there is currently little evidence of the effectiveness of regular surveillance. This they speculate is unlikely to be resolved in the near future due to difficulties in trial design. They also note the development of new ablation techniques but also note the paucity of evidence.
General comments	The quality of the study cannot be fully assessed due to the lack of information surrounding inputs into the model. It is not stated if data sources were chosen systematically and the rationale for any choices made. For sensitivity analysis there is no statement on the distributions used. In addition, the conclusion of cost effectiveness does not seem reasonable without some statement over willingness to pay. Similar studies have utilized a threshold of $50,000. Suggesting that no surveillance to be the most cost effective option.

Full bibliographic reference	Inadomi JM, Somsouk M, Madanick RD et al. (2009) A Cost-Utility Analysis of Ablative Therapy for Barrett's Esophagus. Gastroenterology 136: 2101-14.
Source of funding	National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health and BARRX
Economic study type	Cost-effectiveness analysis conducted using a combined

	decision tree/Markov model.
Population, country and perspective	Patients with BE, LGD and HGD.
Comparison(s)	Strategy 1 – Natural history (no surveillance) Strategy 2 – Endoscopic (surveillance) Strategy 3 – Ablate (surveillance) Strategy 4 – Ablate (no surveillance) Ablation included – RFA, PDT, APC and MPEC.
Source of effectiveness data	States systematic review of published studies. Indicates that values were selected by pooling some values and weighting by study size. Utilities based on Provezale et al 1999, Inadomi 2003, Gerson et al 2005, Fisher 2002, de Boer AG et al 2002 and authors assumptions.
Cost components	Based on US published data sources including Medicare/aid services and ambulatory payment classification and CPT. Additional costs were estimated.
Time horizon, discount rate	Until 80 years or death 3% discount rate for costs, no discounting for benefits
Results – cost	For HGD No Surveillance – US$ 1859 RFA with surveillance – $20776 APC with surveillance – $22117 PDT with surveillance – $34,580 Surveillance – $48,354 Esophagectomy – $58,973
Results – effectiveness	For HGD No Surveillance – 12.43 RFA with surveillance – 15.67 APC with surveillance – 15.62 PDT with surveillance – 15.67 Surveillance – 14.82 Esophagectomy – 15.02
Results – adverse events	For HGD cancers per 100 population No Surveillance – 37.3 RFA with surveillance – 4.0 APC with surveillance – 4.1 PDT with surveillance – 4.3 Surveillance – 7.9 Esophagectomy – 1.8
Results – Incremental cost-effectiveness	For HGD No Surveillance – ref RFA with surveillance – 5839 APC with surveillance – (dominated)

	PDT with surveillance – 32,588,150 Surveillance – (dominated) Esophagectomy – (dominated)
Results – Uncertainty	Result of one-way sensitivity analysis indicates that RFA is preferred ablation therapy is proportion of patients with residual HGD after ablation in <18%, otherwise APC is preferred. If residual HGD after ablation with RFA or APC is greater than 23% then PDT is cost effective at a WTP $100,000 or 30% at WTP $50000. When WTP is <$30,000 then no surveillance is the preferred option otherwise ablation with RFA is the preferred option.
Authors' conclusions	Ablation is the preferred strategy for the management of BE with HGD. The main unknown is whether it is necessary to continue to survey those with BE but no dysplasia. The model indicates that is not cost effective to do so.
General comments	The model structure appears to be appropriate, however the manner in which surveillance is incorporated is unclear. The alteration of clinical effectiveness to match incidence of cancer is not specified. Methodology of pooling values is incorrect. Distributions in PSA not specified.

Full bibliographic reference	Pohl H, Sonnenberg A, Strobel S et al. (2009) Endoscopic versus surgical therapy for early cancer in Barrett's esophagus: a decision analysis. Gastrointestinal Endoscopy 70(4):623-31
Source of funding	Unknown
Economic study type	Cost-effectiveness analysis conducted using a decision tree
Population, Country and perspective	65-year old man with early Barrett's oesophagus carcinoma, USA, payer
Comparison(s)	Endoscopic therapy (EMR and ablation) versus surgical resection.
Source of effectiveness data	Obtained from published literature, numerous studies referenced for each point estimate. Max-min values used in sensitivity analysis For utilities perfect health assumed for health states, assumed from clinician consensus that living with dysphagia was associated with a decrement of 0.03 and from Provenzale et al 1994, Blazeby et al 2000 and Gerson et al 2000 got a value of 0.97 for after surgery.
Cost components	Published US source of costs
Time horizon, discount rate	5 years, no discount rate stated

Results – cost	Endoscopic therapy – $17,408 Surgery – $27,830
Results – effectiveness	Endoscopic therapy – 4.88 Surgery – 4.59
Results – adverse events	N/A
Results – incremental cost-effectiveness	Endoscopic therapy dominates surgery
Results – uncertainty	One-two and three way sensitivity analysis was undertaken. Endoscopy remained the cost effective choice in all scenarios apart from by increasing the dysphagia after endoscopic treatment to 74%< and increasing the lymph node invasion to 69%. For two-way sensitivity analysis surgery became the preferred option where operative mortality was low and risk of lymph node invasion was high or no reduced (health related quality of life) HRQoL after surgery and lymph node invasion to 55% or no reduced HRQoL and low operati.ve mortality. 3 way sensitivity analysis indicated that when operative mortality and lymph node involvement indicated similar results to 2 way sensitivity analysis
Authors' conclusions	The results of our decision analysis suggest that endoscopic therapy is more cost-effective than esophagectomy for esophageal adenocarcinomas confined to the mucosa as well as esophageal adenocarcinomas with superficial infiltration of the submucosa. Endoscopic therapy may be best suited for patients with a priori high surgical risk, such as elderly patients or with patients with comorbid illnesses. The risk of perioperative mortality and postoperative morbidity outweigh the lower risk of recurrence after surgery compared with endoscopic therapy.
General comments	The time horizon is too short. Unclear is systematic review was used to select values. No PSA included. Model structure does not allow long term impacts to be considered. No adverse events for ablation included.

Full bibliographic reference	Comay D, Blackhouse G, Goeree R et al. (2007) Photodynamic therapy for Barrett's esophagus with high-grade dysplasia: A cost-effectiveness analysis. Canadian Journal of Gastroenterology 21: 217-22.
Source of funding	Axcan Pharma Inc (Canada)
Economic study type	Cost-effectiveness analysis conducted using a Markov model.
Population, country and perspective	50 year old men with BE and newly diagnosed HGD, asymptomatic, treatment naïve and fit for surgery.
Comparison(s)	Surgery

	PDT Endoscopic surveillance
Source of effectiveness data	Literature review of clinical studies, mortality estimated from national cancer institute surveillance epidemiology and end results (SEER) database, and life tables All states assigned value of 1 apart from post-surgery based on Provenzale et al 1994
Cost components	Schedule of benefits for physician services under the health insurance act. Goeree et al 2002. PDT costs came from the manufacturer and LHSCCP
Time horizon, discount rate	5 years, 3% (however also states annual discount rate of 30%)
Results – cost	Surveillance - $17,817 Photodynamic therapy - $22,381 Oesophagectomy - $24,963
Results – effectiveness	Surveillance – 12.53 Lys – 11.85 QALYs Photodynamic therapy – 18.14LY – 17.04 QALYs Oesophagectomy – 18.90LY - 15.85 QALYs
Results – adverse events	None reported
Results – incremental cost-effectiveness	ICER ($/LY) / ICER ($/QALY) Surveillance – Reference Photodynamic therapy - $814/$879 Oesophagectomy – $3,379/dominated
Results – uncertainty	PDT had highest probability of being cost effective for WTP threshold over $1,000/QALY and a prob. 0.99 at $25,000/QALY.
Authors' conclusions	PDT is a cost-effective alternative to ESO and continued endoscopic SURV for the management of patients with BE and HGD. Assuming reasonable WTP, PDT is the strategy most likely to be cost-effective for gains in QALYs. However, ultimately, management must still be individualized to the patient, considering his or her preferences and co-morbidities, as well as local examples.
General comments	Analysis limited by lack of surveillance in PDT arm, reasons for choice of variables not given, No consideration of EMR. Limited consideration of natural history of Barrett's. Life years and QALYs given counter-intuitive for 5 year time horizon e.g. 12.53 life years is not possible.

Full bibliographic reference	Shaheen NJ, Inadomi JM, Overholt BF et al. (2004) What is the best management strategy for high grade dysplasia in Barrett's oesophagus? A cost effectiveness analysis.

	Gut 53: 1736-44.
Source of funding	National Institute for Health, the department of veterans affairs, veterans health administration, health services research and development service grant (Inadomi) and a grant from Janssen Pharmaceuticals.
Economic study type	Cost-effectiveness analysis conducted using a combined decision tree/Markov model.
Population, country and perspective	50 year-old white males with high grade dysplasia. No co-morbid conditions.
Comparison(s)	No surveillance Ablation Endoscopic surveillance Oesophagectomy
Source of effectiveness data	Transitions from literature. Various sources referenced, unclear how values chosen. Utilities from published sources Provenzale et al 1999 and De Boer AG et al 2002. Utilities for living in states of endoscopic surveillance were derived from 56 veterans with BO undergoing surveillance at Durham Veterans' Affairs Medical Center using VAS.
Cost components	Based on US published data sources including Medicare/aid services and ambulatory payment classification and CPT
Time horizon, discount rate	Until 80 year-old or death, 3% costs
Results – cost	Costs in US dollars (euros) No preventative strategy – $748 (613) Oesophagectomy – $34,857 (28,583) Endoscopic surveillance – $34,724 (28,474) Endoscopic ablation – $41,998 (34,438)
Results – effectiveness	No preventative strategy – 13.90 Oesophagectomy – 14.89 Endoscopic surveillance – 14.96 Endoscopic ablation – 15.51
Results – adverse events	Cancer per 1000 patients No preventative strategy – 185.4 Oesophagectomy – 2.0 Endoscopic surveillance – 65.2 Endoscopic ablation – 31.6
Results – incremental cost-effectiveness	No preventative strategy – Ref Oesophagectomy – Dominated Endoscopic surveillance – $32,053 (26,283) (extendly dominated) Endoscopic ablation – $25,621 (21,009)
Results – uncertainty	Most sensitive to HGD to Cancer transition. Surgery becomes more cost-effective as transition increases.

	Ablative therapy has to cost less than $15,000 for it to be considered cost-effective. Ablative therapy has a 95% chance of being cost effective at under $50,000 WTP.
Authors' conclusions	Model suggests that endoscopic ablative therapy provides the longest QAL expectancy in subjects with BO and HGD. Endoscopic surveillance has a lower cost than endoscopic ablation but a condition of extended dominance exists such that endoscopic ablation will likely be the therapy of choice for most payers. Surgery is dominated by endoscopic surveillance in the base-case model, and only becomes the favoured strategy at extremely high rates of progression from HGD to cancer.
General comments	Sensitivity analysis limited by lack of distributions and true incremental analysis of sensitivity. No reasoning for choice of values. Only in US. Utilities do not match reference case since a visual analogue tool was used rather than a choice based instrument.

Full bibliographic reference	Hur C, Nishioka NS, Gazelle GS (2003) Cost-effectiveness of photodynamic therapy for treatment of Barrett's esophagus with high grade dysplasia. Digestive Diseases & Sciences 48: 1273-83.
Source of funding	Glaxosmithkline Institute for digestive health.
Economic study type	Cost-effectiveness analysis conducted using a Markov model.
Population, country and perspective	55 year old men, USA, societal, HGD patients
Comparison(s)	Surveillance. Surgery, PDT
Source of effectiveness data	Overholt et al data for PDT. Various other sources referenced, unclear how values were selected. Utilities obtained from expert opinion and Provenzale et al 1999 and Provenzale et al 1994. Plus an assumption of perfect health for post PDT.
Cost components	HCFA, red book and Soni et al 2000, Provenzale et al 1999.
Time horizon, discount rate	Life time time-horizon, 3.00% for benefits and costs
Results – cost	Surveillance - $27,800 Surgery - $41,100 PDT - $48,200
Results – effectiveness	Surveillance – 9.96 Surgery – 9.44 PDT – 11.61
Results – adverse events	Cause of death (%) Surveillance, surgery, PDT Endoscopic complication – 0.03, 0.06, 0.16

	Surgery for HGD – 0, 2.86, 0.91 Surgery for cancer – 1.81, 0, 0.37 Cancer – 20.63, 13.13, 10.14
Results – incremental cost-effectiveness	Surveillance – reference Surgery – Dominated PDT – $12,400
Results – uncertainty	Sensitivity analysis demonstrated that the results for PDT were robust for most scenarios, only long term Qol after PDT made substantial differences to the conclusions. Had to lower than post-surgery.
Authors' conclusions	PDT is a cost-effective therapy for the management of HGD. Further long term follow-up data for PDT are necessary to confirm some of the assumptions in the model, but sensitivity analysis demonstrate that the results are robust
General comments	US setting, societal perspective adopted. No utilities specified for no Barretts oesophagus. No PSA, limited number of transitions for example no regression transitions to LGD presented in diagram or in tables. Limited efficacy data examined compared to other studies.

Full bibliographic reference	Vij R, Triadafilopoulos G, Owens DK et al. (2004) Cost-effectiveness of photodynamic therapy for high-grade dysplasia in Barrett's esophagus. Gastrointestinal Endoscopy 60: 739-56.
Source of funding	NIH, National research service award and agency for healthcare research and quality.
Economic study type	Cost-effectiveness analysis conducted using a combined decision tree/Markov model.
Population, country and perspective	55 year old males with HGD. USA, 3rd party payer
Comparison(s)	Surgery Surveillance PDT and surveillance PDT followed by surgery for HGD
Source of effectiveness data	Numerous published sources referenced, data pooled with random effects model. Utilities from published sources Provenzale et al 1999 and De Boer AG et al 2002 and authors consensus.
Cost components	Based on US published data sources including Medicare/aid services and ambulatory payment classification and CPT
Time horizon, discount rate	Lifetime, 3.00% costs unclear if it applies to utilities

Results – cost	Surgery - $24,045 Surveillance - $28,850 PDT followed by surgery for HGD - $45,525 PDT and surveillance - $47,300
Results – effectiveness	Surgery – 14.419LY 18.817QALYs (doesn't match the accompanying text could potentially be 11.819 but then other results unclear) Surveillance – 14.376LY 11.819QALYs PDT followed by surgery for HGD – 14.756LY 12.243QALYs PDT and surveillance – 14.811LY 12.307QALYs
Results – adverse events	Lifetime results Deaths from: cancer/surgery/endoscopy per 100 Surgery – 6.9/3.97/0 Surveillance – 9.04/3.04/0.027 PDT followed by surgery for HGD – 8.15/1.69/0.038 PDT and surveillance – 8.91/1.21/0.047
Results – incremental cost-effectiveness	Surgery - Surveillance –extended dominated PDT followed by surgery for HGD – extended dominated PDT and surveillance – $47,410
Results – uncertainty	Most important variable was quality of life for HGD. Operative mortality has impact on relative cost effectiveness, if it is low (<2%) then surgery cost effective, if it high then surveillance becomes a cost effective option. Quality of life post surgery greater than 0.85 then both PDT and surveillance become cot effective options.
Authors' conclusions	PDT cost-effective in HGD as long as operative mortality is high, cancer prevalence in HGD is low, or if surgery reduces quality of life. Trials should be conducted in a homogenous population and compare PDT to surgery
General comments	Values for QALYs incorrect. Not clear if parameters chosen systematically, no PSA included.

Full bibliographic reference	Ragunath K, Krasner N, Raman VS et al. (2005) Endoscopic ablation of dysplastic Barrett's oesophagus comparing argon plasma coagulation and photodynamic therapy: A randomized prospective trial assessing efficacy and cost-effectiveness. Scandinavian Journal of Gastroenterology 40: 750-8.
Source of funding	Axcan Pharma – Canada, Cook UK, Wyeth Pharma
Economic study type	Trial based analysis
Population, country and perspective	13 patients with Barrett's oesophagus, LGD and HGD, UK, NHS

Comparison(s)	Argon Plasma coagulation, PDT,
Source of effectiveness data	Trial, no health related quality of life included
Cost components	University Hospital Aintree NHS Trust.
Time horizon, discount rate	1 year follow-up
Results – cost	Cost difference of £1463 PDT being more expensive
Results – effectiveness	APC – 56% Barrett's eradication PDT – 62% Barrett's eradication
Results – adverse events	See clinical trial
Results – incremental cost-effectiveness	£146 per percentage difference in eradication.
Results – uncertainty	95% confidence interval for cost effectiveness £125 to dominating (APC dominates PDT).
Authors' conclusions	PDT more effective than APC but more expensive. Both treatments work
General comments	No QALYs, No consideration of uncertainty, short follow-up, no surveillance, EMR or surgery comparators.

13.4 Quality checklists

An economic analysis of endoscopic ablative therapy for management of non-dysplastic Barrett's oesophagus **A Das et al 2009**		
Guideline topic: Barrett's oesophagus	Question no:	
Check list completed by Prashanth Kandaswamy		
Section 1: Applicability	**Yes/ Partly/ No/ Unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the guideline?	No	Only considered non-dysplastic Barrett's.
1.2 Are the interventions appropriate for the guideline?	Partly	No EMR or only surgery option
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	US setting resource use likely to be different
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	No	US perspective
1.5 Are all direct health effects on individuals included?	Yes	
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	3% for costs unclear if any discount for utilities.

1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Partly	The studies referenced directly elicited values from patients
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	Valued by patients
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Not applicable		
Other comments		

Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline*	**Yes/Partly/No/ Unclear/NA Comments**	**Comments**
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant health outcomes included?	Partly	No utility for perferoration or for undergoing surgery
2.4 Are the estimates of baseline health outcomes from the best available source?	unknown	No systematic review presented
2.5 Are the estimates of relative treatment effects from the best available source?	Unknown	No systematic review presented
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	No	Cost of ablation therapy was a conservative estimate
2.8 Are the unit costs of resources from the best available source?	No	From US sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Unknown	Distributions not stated
2.11 Is there no potential conflict of interest?	Unknown	None mentioned
2.12 **Overall assessment**: Minor limitations/Potentially serious limitations/Very serious limitations		

Potentially serious limitations

A cost-utility of ablative therapy for Barrett's oesophagus **Inadomi et al 2009**		
Guideline topic: Barrett's oesophagus	Question no:	
Check list completed by Prashanth Kandaswamy		
Section 1: Applicability	**Yes/ Partly/ No/ Unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the guideline?	Yes	
1.2 Are the interventions appropriate for the guideline?	Partly	Missing EMR and only surgery
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	US setting resource use likely to be different
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	No	US perspective
1.5 Are all direct health effects on individuals included?	Yes	
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	3% discount used for costs unclear if similar used for benefits
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Partly	Elicited directly from patients
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	Elicited directly from patients
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Partially applicable		
Other comments		

Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline*	**Yes/Partly/No/ Unclear/NA** **Comments**	**Comments**
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	

2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant health outcomes included?	Partly	More adverse events would be better
2.4 Are the estimates of baseline health outcomes from the best available source?	No	Estimates calculated by pooling data and weighting by sample size, is inappropriate given the quality of the data
2.5 Are the estimates of relative treatment effects from the best available source?	No	Estimates calculated by pooling data and weighting by sample size, is inappropriate given the quality of the data
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	No	From US sources
2.8 Are the unit costs of resources from the best available source?	No	From US sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Unknown	No distributions for PSA
2.11 Is there no potential conflict of interest?	No	Barxx Funding
2.12 Overall assessment: Minor limitations/Potentially serious limitations/Very serious limitations Very serious limitations		

Endoscopic versus surgical therapy for early cancer in Barrett's oesophagus: a decision analysis **Pohl H et al 2009**		
Guideline topic: Barrett's oesophagus		Question no:
Check list completed by Prashanth Kandaswamy		
Section 1: Applicability	**Yes/ Partly/ No/ Unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the guideline?	No	Early Barrett's rather than HGD
1.2 Are the interventions appropriate for the guideline?	No	Does not include ablation
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	US setting resource use likely to be different
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	No	US perspective

1.5 Are all direct health effects on individuals included?	No	No long term effects
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	None stated
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Partly	Elicited from patients with standard gamble technique
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	Elicited from patients with standard gamble technique
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Not applicable		
Other comments		

Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline*	**Yes/Partly/No/ Unclear/NA Comments**	**Comments**
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	No	Does not consider progressive nature of condition
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	No	5 year time horizon
2.3 Are all important and relevant health outcomes included?	Partly	Long term effects such as recurrence of cancer are not included
2.4 Are the estimates of baseline health outcomes from the best available source?	Unknown	Unclear what rationale was used for selecting values
2.5 Are the estimates of relative treatment effects from the best available source?	Unknown	Unclear what rationale was used for selecting values
2.6 Are all important and relevant costs included?	Partly	No long term costs
2.7 Are the estimates of resource use from the best available source?	No	US setting resource use likely to be different
2.8 Are the unit costs of resources from the best available source?	No	US perspective
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Partly	Values elicited from standard gamble estimates from patients
2.10 Are all important parameters whose values are uncertain subjected	No	Time horizon was not subject to sensitivity

to appropriate sensitivity analysis?		analysis and no probabilistic sensitivity analysis undertaken
2.11 Is there no potential conflict of interest?	Unknown	No source of funding given
2.12 Overall assessment: Minor limitations/Potentially serious limitations/Very serious limitations Very serious limitations		
The time horizon is a major issue for this lifelong condition		

Photodynamic therapy for Barrett's oesophagus with high-grade dysplasia: A cost effectiveness analysis **Comay D, et al 2007**		
Guideline topic: Barrett's oesophagus		Question no:
Check list completed by Prashanth Kandaswamy		
Section 1: Applicability	**Yes/ Partly/ No/ Unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the guideline?	Yes	
1.2 Are the interventions appropriate for the guideline?	No	No EMR included
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	Canada setting resource use likely to be different
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	No	Canadian perspective
1.5 Are all direct health effects on individuals included?	Yes	
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	3% for both costs and benefits
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Partly	Assume perfect health for most states
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Partly	Assume perfect health for most states
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Not applicable		
Other comments		
Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has been decided that the study is sufficiently applicable*	**Yes/Partly/No/ Unclear/NA Comments**	**Comments**

to the context of the clinical guideline		
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	No	Natural history absent
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	No	Only five year time horizon, insufficient for long-term condition
2.3 Are all important and relevant health outcomes included?	Partly	No adverse events
2.4 Are the estimates of baseline health outcomes from the best available source?	Unknown	Partial literature review carried out unclear how values were chosen
2.5 Are the estimates of relative treatment effects from the best available source?	Unknown	Partial literature review carried out unclear how values were chosen
2.6 Are all important and relevant costs included?	Partly	Treating perforations excluded
2.7 Are the estimates of resource use from the best available source?	No	Canadian sources used
2.8 Are the unit costs of resources from the best available source?	No	Canadian sources used
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Is there no potential conflict of interest?	No	Pharma funding
2.12 Overall assessment: Minor limitations/Potentially serious limitations/Very serious limitations Potentially serious limitations		

What is the best management strategy for high grade dysplasia in Barrett's oesophagus? A cost effectiveness analysis Shaheen et al 2004		
Guideline topic: Barrett's oesophagus		Question no:
Check list completed by Prashanth Kandaswamy		
Section 1: Applicability	**Yes/ Partly/ No/ Unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the guideline?	Yes	
1.2 Are the interventions appropriate for the guideline?	Partly	No EMR included

1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	US setting resource use likely to be different
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	No	US perspective
1.5 Are all direct health effects on individuals included?	Partly	Not all AEs utility
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	3% for costs unclear if same applied for utilities
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Partly	Visual analogue scale was filled in by patients, not in reference case
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	Visual analogue scale was filled in by patients, not in reference case
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Not applicable		
Other comments		

Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline*	**Yes/Partly/No/ Unclear/NA Comments**	**Comments**
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant health outcomes included?	No	Adverse events for stricture are no included
2.4 Are the estimates of baseline health outcomes from the best available source?	Unknown	Not clear from paper how values were selected.
2.5 Are the estimates of relative treatment effects from the best available source?	Unknown	Not clear from paper how values were selected.
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	No	US sources used
2.8 Are the unit costs of resources from the best available source?	No	US sources used
2.9 Is an appropriate incremental	Yes	

analysis presented or can it be calculated from the data?		
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No distributions for PSA presented
2.11 Is there no potential conflict of interest?	No	Pharma funding
2.12 Overall assessment: Minor limitations/Potentially serious limitations/Very serious limitations Potentially serious limitations		

Cost-effectiveness of photodynamic therapy for treatment of Barrett's oesophagus with high grade dysplasia **Chin Hur et al 2003.**		
Guideline topic: Barrett's oesophagus		Question no:
Check list completed by Prashanth Kandaswamy		
Section 1: Applicability	**Yes/ Partly/ No/ Unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the guideline?	Yes	
1.2 Are the interventions appropriate for the guideline?	Partly	No EMR included
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	US setting resource use likely to be different
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	No	US societal perspective
1.5 Are all direct health effects on individuals included?	Yes	
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	3% used for costs but 30% also referenced
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Partly	Visual analogue scale was filled in by patients, not in reference case
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	Visual analogue scale was filled in by patients, not in reference case
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Partially applicable		

Other comments		
Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline*	**Yes/Partly/No/ Unclear/NA Comments**	**Comments**
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	Partly	Limited number of transitions for example no regression to LGD
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant health outcomes included?	Yes	
2.4 Are the estimates of baseline health outcomes from the best available source?	No	No indication of systematic review for selection of values
2.5 Are the estimates of relative treatment effects from the best available source?	No	No indication of systematic review for selection of values
2.6 Are all important and relevant costs included?	Partly	Treatment of adverse events not included
2.7 Are the estimates of resource use from the best available source?	No	US sources
2.8 Are the unit costs of resources from the best available source?	No	US sources
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No probabilistic sensitivity analysis carried out
2.11 Is there no potential conflict of interest?	No	GSK funding
2.12 **Overall assessment**: Minor limitations/Potentially serious limitations/Very serious limitations Potentially serious limitations		

Cost effectiveness of photodynamic therapy for high-grade dysplasia in Barrett's eosophagus **Vij et al 2004**		
Guideline topic: Barrett's oesophagus		Question no:
Check list completed by Prashanth Kandaswamy		
Section 1: Applicability	**Yes/ Partly/ No/**	**Comments**

	Unclear/ NA	
1.1 Is the study population appropriate for the guideline?	Yes	
1.2 Are the interventions appropriate for the guideline?	Partly	EMR not included
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Partly	US setting resource use likely to be different
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	No	US perspective
1.5 Are all direct health effects on individuals included?	Partly	AE from treatment
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	3% for costs unclear if similar used for utilities
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Partly	Elicited directly from patients via a standard gamble tool
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	Elicited directly from patients via a standard gamble tool
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Partially applicable		
Other comments		

Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline*	**Yes/Partly/No/ Unclear/NA Comments**	**Comments**
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant health outcomes included?	Yes	
2.4 Are the estimates of baseline health outcomes from the best available source?	No	Pooled data with random effects model, considered inappropriate given the quality of the data
2.5 Are the estimates of relative treatment effects from the best available source?	No	Pooled data with random effects model, considered inappropriate given the quality of the data

2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	No	US sources used
2.8 Are the unit costs of resources from the best available source?	No	US sources used
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No probabilistic sensitivity analysis carried out
2.11 Is there no potential conflict of interest?	Yes	
2.12 **Overall assessment**: Minor limitations/Potentially serious limitations/Very serious limitations Very serious limitations		

Endoscopic ablation of dysplastic Barrett's oesophagus comparing argon plasma coagulation and photodynamic therapy: A randomized prospective trial assessing efficacy and cost-effectiveness **Ragunath et al 2004**		
Guideline topic: Barrett's oesophagus		Question no:
Check list completed by Prashanth Kandaswamy		
Section 1: Applicability	**Yes/ Partly/ No/ Unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the guideline?	Partly	Includes LGD
1.2 Are the interventions appropriate for the guideline?	No	No surveillance, EMR or surgery
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5 Are all direct health effects on individuals included?	No	No quality of life included
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	No	No discounting
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	No	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	No	
1.9 Is the valuation of changes in HRQoL	No	

(utilities) obtained from a representative sample of the general public?		
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Not applicable		
Other comments		
Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline*	**Yes/Partly/No/ Unclear/NA Comments**	**Comments**
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	N/A	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	No	Time horizon is too short for life long condition
2.3 Are all important and relevant health outcomes included?	No	No quality of life included
2.4 Are the estimates of baseline health outcomes from the best available source?	Partly	No quality of life included
2.5 Are the estimates of relative treatment effects from the best available source?	Yes	Trial based
2.6 Are all important and relevant costs included?	Unknown	Not presented
2.7 Are the estimates of resource use from the best available source?	Partly	Hospital specific
2.8 Are the unit costs of resources from the best available source?	Partly	Hospital specific
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	No	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	
2.11 Is there no potential conflict of interest?	No	Pharma
2.12 **Overall assessment**: Minor limitations/Potentially serious limitations/Very serious limitations Very serious limitations		

13.5 GRADE table of ablative cost effectiveness studies

Study	Population	Comparators	Costs (£)	QALYS	Incremental QALYS	Incremental costs	ICER (incremental)	Uncertainty	Limitations	Applicability
A Das et al 2009	Non dysplastic Barrett's oesophagus, 50 year old males	Natural history (no surveillance)	1898.5[1]	17.959	Reference			Under a willingness to pay threshold of £39360 no surveillance is most cost effective treatment option. At thresholds greater than £60,000 ablation is most cost effective.	Potentially serious limitations	Not applicable
		Endoscopic (surveillance)	8538.5	18.076	0.117	6640	56700.7			
		Ablate (HALO ablation system) (surveillance)	14378.9	18.259	0.3	12480.4	41600.9 (31898.7)			
	Comments: US based study. Did not include patients with dysplasia, EMR and surgery were not considered as comparators, 3% discount rate used for costs. Estimates for efficacy are not based on a systematic review of the data.									
Inadomi et al 2009	Patients with Barrett's oesophagus, with low grade dysplasia (LGD) and high grade dysplasia (HGD). Only HGD results reported	Natural history (no surveillance)	1219.5	12.43	Reference			Ablation is preferred option at WTP thresholds over £32800. Under £19680 no surveillance is preferred.	Very serious limitations	Not applicable
		RFA with surveillance	13629.1	15.67	3.24	12409.6	3830.4			
		APC with surveillance	14508.8	15.62	3.19	13289.2	dominated			
		PDT with surveillance	22684.5	15.67	3.24	14905	21377826.4			
		Endoscopic (surveillance)	31720.2	14.82	2.39	30500.7	dominated			

[1] Converted to UK pounds from US dollars using a PPP exchange rate of 0.656 (www.oecd.org/std/ppp)

Study	Population	Comparators	Costs (£)	QALYS	Incremental QALYS	Incremental costs	ICER (incremental)	Uncertainty	Limitations	Applicability
		Esophagectomy	38686.3	15.02	2.59	37466.8	dominated			
	Comments: US based study; certain clinical parameters were calculated by pooling data from a number of studies and weighting by sample size. EMR not included.									
Pohl H et al 2009	65-year old men with early Barrett's oesophagus carcinoma,	Endoscopic therapy	11419.7	4.88	Reference			Deterministic sensitivity analysis undertaken surgery is only preferred when percentage of dysphagia after endoscopic treatment is over 74% or is lymph node invasion percentage is over 69%	Very serious limitations	Not applicable
		Surgical resection	18256.5	4.59	-0.29	68396.6	dominated			
	Comments: US study, does not include ablation, time horizon too short (5 years)									
Comay D, et al 2007	50 year old men with Barrett's oesophagus and newly diagnosed HGD,	Endoscopic surveillance	11688	11.85	Reference			PDT had highest prob. of being cost effective for WTP threshold over £656/QALY and a prob. 0.99 at £16400/QALY.	Potentially serious limitations	Not applicable
		PDT	14682	17.04	5.19	2994	576.6			
		Surgery	16375.7	15.85	4.00	4687.8	dominated			
	Comments: Canadian based study, 5 year time horizon is insufficient for life time condition and QALY estimates are counter intuitive for example 15.85 QALYs over 5 years.									
Shaheen et al 2004	50 year-old males with	No surveillance	490.7	13.90	Reference			Ablative therapy had a 95%	Potentially serious	Not applicable

Study	Population	Comparators	Costs (£)	QALYS	Incremental QALYS	Incremental costs	ICER (incremental)	Uncertainty	Limitations	Applicability
	HGD	Endoscopic surveillance	22778.9	14.96	1.06	22288.3	21026.8 (extended dominated)	chance of being cost effective at under £32800 WTP.	limitations	
		Oesophagectomy	22866.2	14.89	0.99	22375.5	Dominated			
		Ablation	27550.7	15.51	0.61	27060	16807.4			
	Comments: US based study, EMR not included, 3% discount rate used for costs, unclear from paper how parameters were chosen.									
Chin Hur et al 2003	55 year old HGD patients	Surveillance	18236.8	9.96	Reference			If long term utility after PDT lower than post-surgery utility surveillance was preferred option.	Very serious limitations	Not applicable
		Surgery	26961.6	9.44	-0.52	8724.8	Dominated			
		PDT	31619.2	11.61	1.65	13382.4	8134.4			
	Comments: US based study. EMR not included. 3% and 30% discount rates mentioned in paper. No systematic review for selection of parameters. Utilities elicited from patients using visual analogue scale, which is prone to bias over a choice based instrument.									
Vij et al 2004	55 year old males with HGD	Surgery	15773.5	11.819	Reference			Several deterministic analyses undertaken indicated that surgery is preferred option if operative mortality is below 2%, as it increased surveillance and PDT become more cost effective options.	Very serious limitations	Not applicable
		Surveillance	18925.6	Incorrect number reported	Incorrect number reported	3152.1	Extended dominated			
		PDT and surveillance	29864.4	12.243	0.424	14090.9	Extended dominated			
		PDT followed by surgery for HGD	31028.8	12.307	0.488	15255.3	31101			

Study	Population	Comparators	Costs (£)	QALYS	Incremental QALYS	Incremental costs	ICER (incremental)	Uncertainty	Limitations	Applicability
	Comments: US based study. EMR not included. 3% discount rate for costs. Estimates for health outcomes were derived from random effects model, considered inappropriate due to quality of data.									
Ragunath et al 2004	13 patients with Barrett's oesophagus, LGD and HGD	Argon plasma coagulation,	None	None	None	None	None	None	Very serious limitations	Not applicable
		PDT	None	None	None	1463	None			
	Comments: No appropriate comparators, no incremental analysis. No health related quality of life considerations.									

13.6 Review of Garside et al 2006

The reports objective was to identify what was known about the clinical and cost effectiveness of surveillance in Barrett's oesophagus and in addition identify key areas of uncertainty for future research. For their analysis the Health Technology Assessment (HTA) group carried out an extensive systematic review of clinical data following guidelines from NCCHTA. In addition a workshop was carried out with experts to identify key areas of uncertainty. A de novo model was constructed that estimates the incremental cost and QALY gain for endoscopic surveillance in 1000 55 year old men with Barrett's oesophagus over a 20 year time horizon. Costs were derived from NHS reference costs. Utilities were derived from the value of health panel a group of 64 people from the general population who were given scenarios and then use standard gamble techniques for eliciting values. The model structure is shown in figure 10 (figure 1 in original report) below:

Figure 11 Model structure from Garside et al 2006

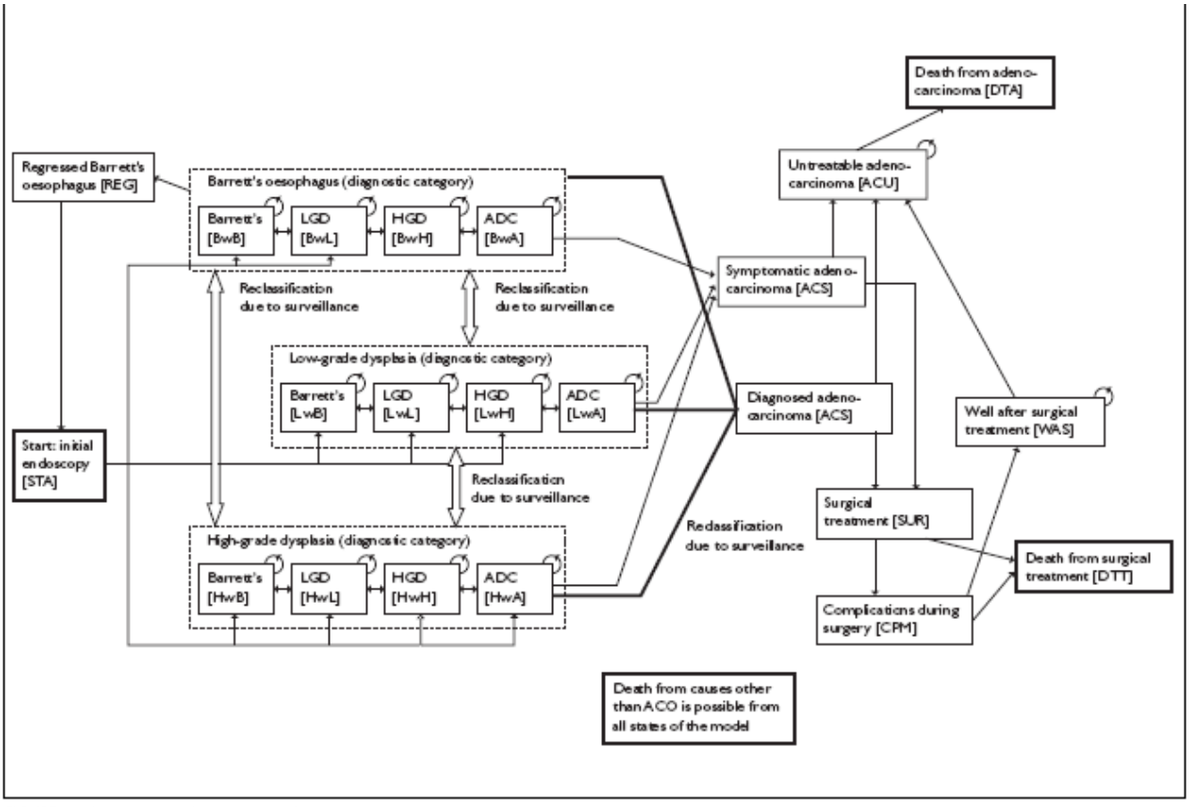


FIGURE 1 Influence diagram for patients with Barrett's oesophagus

In this model patients are allocated to a state based on a initial endoscopy into BO, LGD and HGD. Patients can then progress/regress in each diagnostic state and will stay there until surveillance picks them up and are re-classified or until they develop cancer. If there is no surveillance then cancer is only picked up when symptoms appear. If surveillance is present then it can be picked up when it is asymptomatic. Patients with cancer undergo surgery if possible of are treated as untreatable cancer. If surgery is successful patients stay in a well after surgery state with no prospect of relapsing to Barrett's. However, they can get cancer again. Death from other causes is based on age related mortality.

This model does not include misdiagnosis from surveillance, but allows a initial misdiagnosis. This is because the Garside et al 2006 considered that the natural history data contains artefacts of misdiagnosis.

It is assumed by Garside et al 2006 that all the progression rates obtained via surveillance remains true even when there is no surveillance and also the progression is a linear function between the observed states. In addition,

patients progress through each state sequentially. This they comment may not reflect reality but they do this given the quality of the data and its limitations.

Also the annual progression rte to cancer was assumed to be constant. Whereas it may be assumed that if no progression is viewed in the first year then the chance of progression in the second year is reduced.

There is the assumption that all progression rates and incidences are constant, in reality this would change given the aging of the cohort.

The results of this analysis are summarised in the table below:

Table 49 Deterministic results from Garside et al 2006

Treatment	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER
Endoscopic surveillance	3869048	11983			
No surveillance	2951230	12029	917818	48	Dominates

Garside et al 2006 concluded that surveillance produces fewer QALYs and costs more than no surveillance. Thereby no surveillance dominates surveillance. The cost per cancer identified was estimated as £45,000 in the surveillance arm and the analysis indicated that there was no survival benefit. This was due to high recurrence rates and increased mortality due to more surgical interventions. The HTA found that the variables that the results were most sensitive to were rate of recurrence of cancer after surgery, the rate at which cancer became symptomatic once it has been developed and the utility values attached to the health states. PSA indicated that it was unlikely that surveillance would be cost effective.

The results of the EVPI indicate that if it is assumed that this technology is assumed to be relevant over 10 years a value of £6.5 million is placed on acquiring perfect information.

Conclusion

The overall quality of the report was very high and all assumptions and variables justified. The possible limitations of the report include that the

population examined was a mixture of people with Barrett's oesophagus, LGD and HGD, with only a minority being HGD. The population for this analysis will be only HGD. In addition, the results were not disaggregated which results in difficulty in identifying any difference between this analysis and others. However, there appears to be no major limitations.

	Study name Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling **R Garside, M Pitt, M Somerville, K Stein, A price, and N Gilbert.**	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes?	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	From systematic review and additional published studies
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Brief details given in table of variables

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Due to lack of RCT evidence no meta-analysis was conducted, but means of identified data used.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	HTA group conducted primary evidence gathering from a value of health panel, matches NICEs reference case
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	Use of NHS reference costs implies that there is no requirement to separately calculate unit costs as all costs are included in estimate
17. Were the methods for the estimation of quantities and unit costs described?	Yes	NHS reference cost codes quoted
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	No justification is given for the use of a Markov model. However, justification for carrying out De Novo analysis is stated and the model parameters used
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	Old treasury rates of 6% for costs and 1.5% for benefits

25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes/No	For clinical benefits some mid points were stated however, no breakdown of final results was quoted
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

13.7 EORTC-30 to EQ-5D

In table 49 the EORTC-30 figures from Barbour et al 2008 for baseline and post 6 months after surgery are presented and the subsequent results from the conversion in Mackenzie et al 2009

Table 50 Converting EORTC-30 to EQ-5D

Baseline results			
	EORTC-30	Coefficient	Result
Physical	89	0.0004	0.0356
role	80	0.0022	0.176
Emotional	76	0.0028	0.2128
Cognitive	87	0.0009	0.0783
Overall Qol	74	0.0016	0.1184
Fatigue	26	-0.0021	-0.0546
Pain	13	-0.0024	-0.0312
Constant		0.2376	
EQ-5D value			0.7729
6 months post surgery			
Physical	74	0.0004	0.0296
role	61	0.0022	0.1342
Emotional	81	0.0028	0.2268
Cognitive	83	0.0009	0.0747
Overall Qol	66	0.0016	0.1056
Fatigue	40	-0.0021	-0.084
Pain	29	-0.0024	-0.0696
Constant		0.2376	
EQ-5D value			0.6549

The difference between these two values is 0.118 and this will be used as the decrement for surgery.

13.8 References used for resource use in ablation and natural history papers

Reference	Studies where used
CMS 2001-2009	Gerson et al 2007a & 2004 Rubenstein 2007 Pohl et al 2009 Inadomi et al 2009 Vij et al 2004 Shaheen et al 2004 Chin Hur 2004
Provenzale 1994	Inadomi et al 2009 & 2003 Shaheen et al 2004 Rubenstein 2004 Das et al 2009
Provenzale 1999	Inadomi et al 2009 &2003 Shaheen et al 2004 Rubenstein 2004
Soni et al 2000	Inadomi et al 2009 & 1993 Shaheen et al 2004 Rubenstein 2004 Chin Hur 2004 & et al 2003
Gorelick et al 2001	Inadomi et al 2009 &1993 Rubenstein 2004
HCFA	Chin Hur et al 2003
Red Book	Chin Hur et al 2003
LHSCCP, schedule of benefit for physician services under the health insurance act	Comay et al 2004
Soni and Sonnenberg Healthcare resource utilization in the management of esophageal adenocarcinoma 2001 Aliment Pharmacol Ther 2001; 15:945-51	Sonnenberg et al 2002 &03
US dept of health and human services. National and state stats on hospital stay by payer	Pohl et al 2009
Goree et al 2002 schedule of benefit for physician services under the health insurance act	Comay et al 2007
University Hospital Aintree costs	Ragunath et al 2005
Medical University of South Carolina	Nietert et al 2003

13.9 PPI costs

Drug	Dosage	Pack size	Cost	Cost per month
Esomeprazole	20mg daily for control	28 pack of 20mg pills	BNF 58 - £18.50	£20.15
Lansaprazole	15-30mg daily	28 pack 15mg 28 pack 30mg	Dmit – £0.87 Dmit – £1.50	£0.95 £1.63
Oneprazole	20mg daily	28 pack 20mg	Dmit – £0.75	£0.82
Pentoprazole	80mg daily 2 doses a day	28 pack 40mg	BNF 58– £20.57	£44.81
Rabprazole	10mg daily	28 pack 10mg	BNF 58– £11.56	£12.59

Average monthly cost of the six drugs is £13.49 the mid-point is £22.82. The value from Garside et al 2006 of £22 will be used in the model.

13.10 Deterministic sensitivity analysis

		Surveillance	Surgery	EMR	RFA	PDT	EMR + RFA	EMR + PDT	EMR +APC
Base case	values	35277	5560	13846	24829	23002	13990	17327	12300
Cost discount	6%	30985	5529	12301	23672	21725	13257	16480	11375
	1.50%	39807	5640	15516	26165	24456	14826	18307	13315
Utility discount	6%	48685	7907	18603	33610	31202	18856	23440	16599
	1.50%	26525	4054	10589	18863	17457	10654	13166	9362
Untreatable cancer to dead	78.00%								
	39.00%	35522	2562	12994	23987	22118	12814	16162	11110
Well post early cancer surgery to early cancer	9.23%								
	4.62%	12466	5560	7926	16119	14656	10005	12410	8487
	13.85%	-1220174	5560	23743	36554	34669	18213	22635	16577
Well post HGD surgery to early cancer	1.00%								
	0.50%	35277	3698	13846	24829	23002	13990	17327	12300
	1.50%	35277	9046	13846	24829	23002	13990	17327	12300
Well post late cancer surgery to early cancer	26.00%								
	13.00%	70445	6768	18062	30579	28659	16457	20470	14705
	39.00%	28534	5130	12476	22826	21060	13077	16171	11428
Utilities									
Cancer (late)	0.675								
	1	36229	5605	14010	25072	23238	14095	17462	12400
	0.3375	34340	5514	13680	24583	22763	13882	17189	12198
well	0.863								
	1	21789	2668	11222	21043	19343	12457	15384	10815
	0.4315	-37144	-2303	52551	57299	56922	22843	28773	21680

	0.5								
	0.75	35241	5555	13840	24823	22995	13987	17324	12298
complication	0.25	35314	5565	13851	24836	23009	13992	17330	12303
	0.4								
	0.6	35219	5623	13897	24940	23106	14062	17420	12363
untreatable	0.2	35336	5498	13794	24720	22899	13919	17235	12239
No treatment effect	1	34317	5412	13366	24162	22348	13714	16971	12032
No adverse event	1	35277	5560	13845	24828	22932	13988	17321	12293
Costs									
	579								
	869	35277	5560	14513	24829	23002	14413	17769	12764
EMR	290	35277	5560	13181	24829	23002	13569	16887	11838
	770								
	1154	35277	5560	13846	24829	24296	13990	18302	12300
Ablation capital costs per month - PDT	385	35277	5560	13846	24829	21709	13990	16352	12300
	770								
	1154	35277	5560	13846	26255	23002	14613	17327	12300
Ablation capital costs per month - RFA	385	35277	5560	13846	23404	23002	13367	17327	12300
	128								
	192	35277	5560	13846	24829	23002	13990	17327	12470
Ablation capital costs per month - APC	64	35277	5560	13846	24829	23002	13990	17327	12129
	3963								
	5944	35277	5560	13846	32178	23002	17199	17327	12300
RFA	1981	35277	5560	13846	17481	23002	10781	17327	12300
	1321								
	1982	35277	5560	13846	24829	23002	13990	17327	14061
APC	661	35277	5560	13846	24829	23002	13990	17327	10541
	3503								
	5254	35277	5560	13846	24829	28894	13990	21769	12300
PDT	1751	35277	5560	13846	24829	17110	13990	12885	12300
	22								
	33	34645	4411	13657	24706	22872	13934	17275	12230
PPI	11	35909	6709	14034	24953	23133	14046	17380	12371
	6706								
	10059	35277	8153	13956	24914	23040	14103	17356	12381
Surgery	3353	35277	2967	13735	24745	22964	13877	17299	12220
	7516.281128								
	11274.42169	37960	5131	14696	25458	23727	14332	17780	12744
Surgery (A)	3758.140564	32594	5989	12996	24201	22278	13648	16875	11856
	3.31								
	4.965	35486	5527	13912	24878	23059	14016	17362	12335
Excess days	1.655	35069	5593	13780	24781	22946	13963	17292	12266
	176.4474706								
Excess day cost	264.6712059	35486	5527	13912	24878	23059	14016	17362	12335

	88.22373529	35069	5593	13780	24781	22946	13963	17292	12266
	2032.428407								
	3048.642611	35404	4702	13562	24490	22658	13599	16919	11915
Untreatable cancer	1016.214204	35150	6418	14129	25169	23346	14381	17736	12686
	43.08899889								
	64.63349834	36741	8123	14399	25255	23450	14281	17626	12625
Post surgerical well	21.54449945	33814	2997	13293	24404	22555	13699	17029	11976
	517								
	775.5	49162	5560	19036	29196	27714	17030	20752	15740
endoscopy	258.5	21393	5560	8656	20463	18290	10949	13902	8861
	2583								
	3874.5	35390	5620	13868	24846	23020	14001	17338	12313
Complications	1291.5	35165	5501	13823	24813	22984	13979	17316	12288
	703								
	1054.5	35277	5560	13849	24838	23147	14004	17354	12383
Stricture	351.5	35277	5560	13842	24821	22857	13976	17300	12218
	2000								
	3000	35277	5560	13846	28538	23002	15610	17327	12300
RFA consumable	1000	35277	5560	13846	21121	23002	12370	17327	12300
	1540								
Photo sensitising drugs	2310	35277	5560	13846	24829	25592	13990	19280	12300
	770	35277	5560	13846	24829	20412	13990	15374	12300
	404								
	606	35358	5547	13871	24848	23024	14000	17341	12314
Chemotherapy	202	35196	5573	13820	24811	22980	13980	17314	12287
	0.56								
Proportion who receive chemotherapy	0.84	35358	5547	13871	24848	23024	14000	17341	12314
	0.28	35196	5573	13820	24811	22980	13980	17314	12287
	58								
	232	44623	5560	17739	28414	26759	16572	20339	15357
Pathology	29	33720	5560	13197	24232	22376	13560	16825	11791
	60000								
Purchase Price - PDT	90000	35277	5560	13846	26256	24297	14613	18303	12300
	30000	35277	5560	13846	23403	21708	13367	16351	12300
	10000								
Purchase Price - APC	15000	35277	5560	13846	24829	23002	13990	17327	12471
	5000	35277	5560	13846	24829	23002	13990	17327	12129
	7.5								
Life span of technologies	11.25	35277	5560	13846	23998	22248	13627	16759	12201
	3.75	35277	5560	13846	27338	25278	15085	19043	12601
	0.00001								
Resale value	2000	35277	5560	13846	24756	22936	13958	17277	12248

Upper estimates for transition matrix

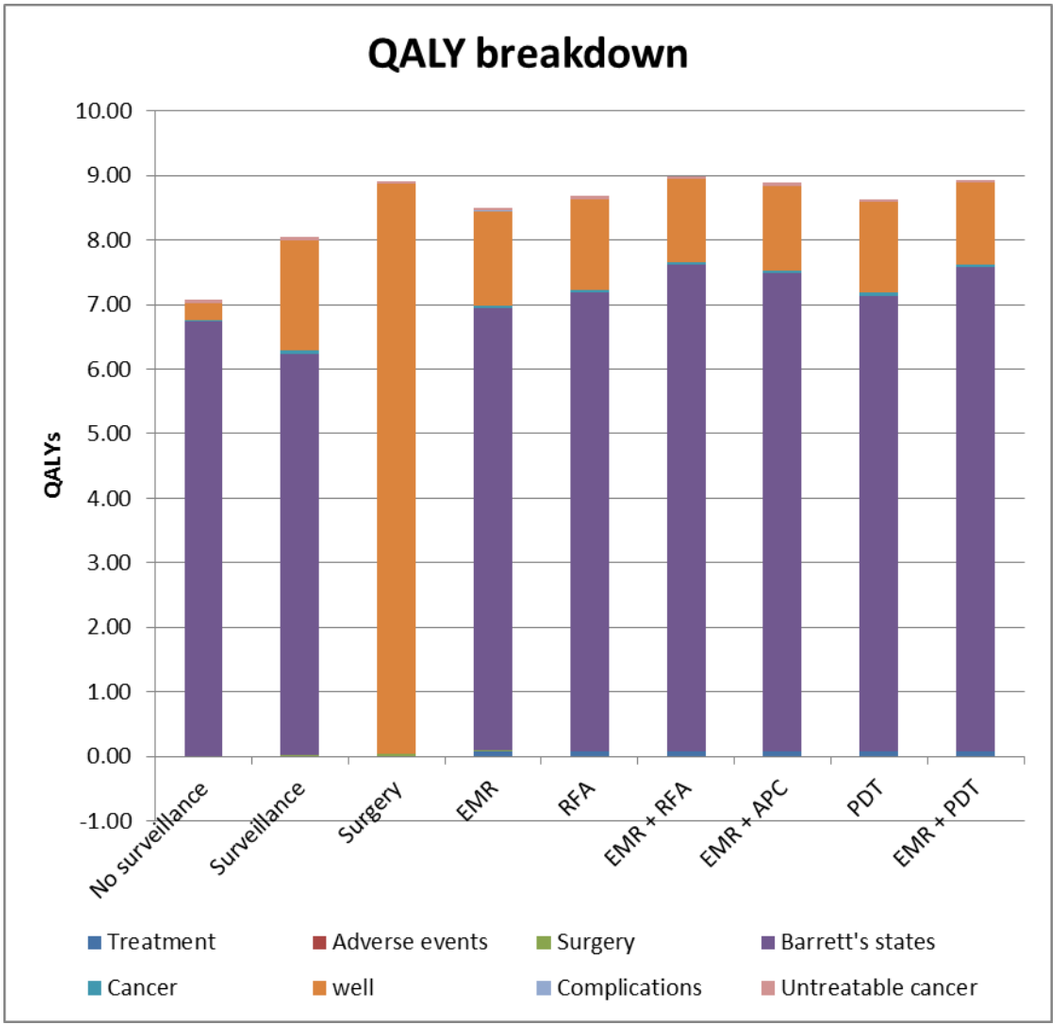
	NBO	Bar	LGD	HGD	Cana	Cans	Dead
NBO	#	0.005	0	0	0	0	Age
Bar	0.0243	#	0.065	0.015	0.005	0	Age
LGD	0.05	0.63	#	0.165	0.04	0	Age
HGD	0	0.1	0.163	#	0.1187	0	Age
Cana	0	0	0	0	#	0.143	Age
Cans	0	0	0	0	0	#	0.78
Dead	0	0	0	0	0	0	1

Lower estimates for transition matrix

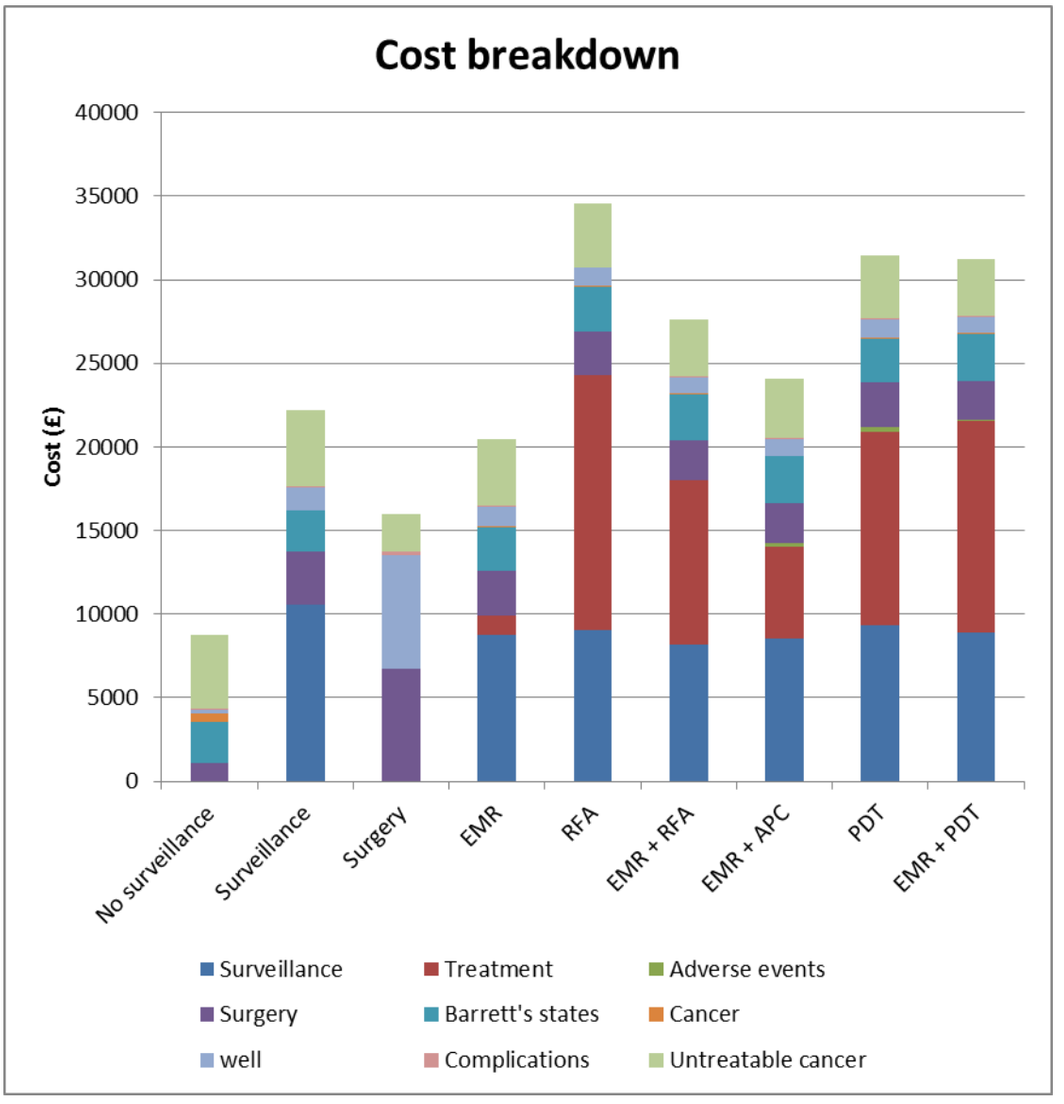
	NBO	Bar	LGD	HGD	Cana	Cans	Dead
NBO	#	0	0	0	0	0	Age
Bar	0.0175	#	0.0275	0	0	0	Age
LGD	0	0.002	#	0.0215	0	0	Age
HGD	0	0	0.0385	#	0.025	0	Age
Cana	0	0	0	0	#	0.14	Age
Cans	0	0	0	0	0	#	0.28
Dead	0	0	0	0	0	0	1

13.11 Breakdown of utilities and costs

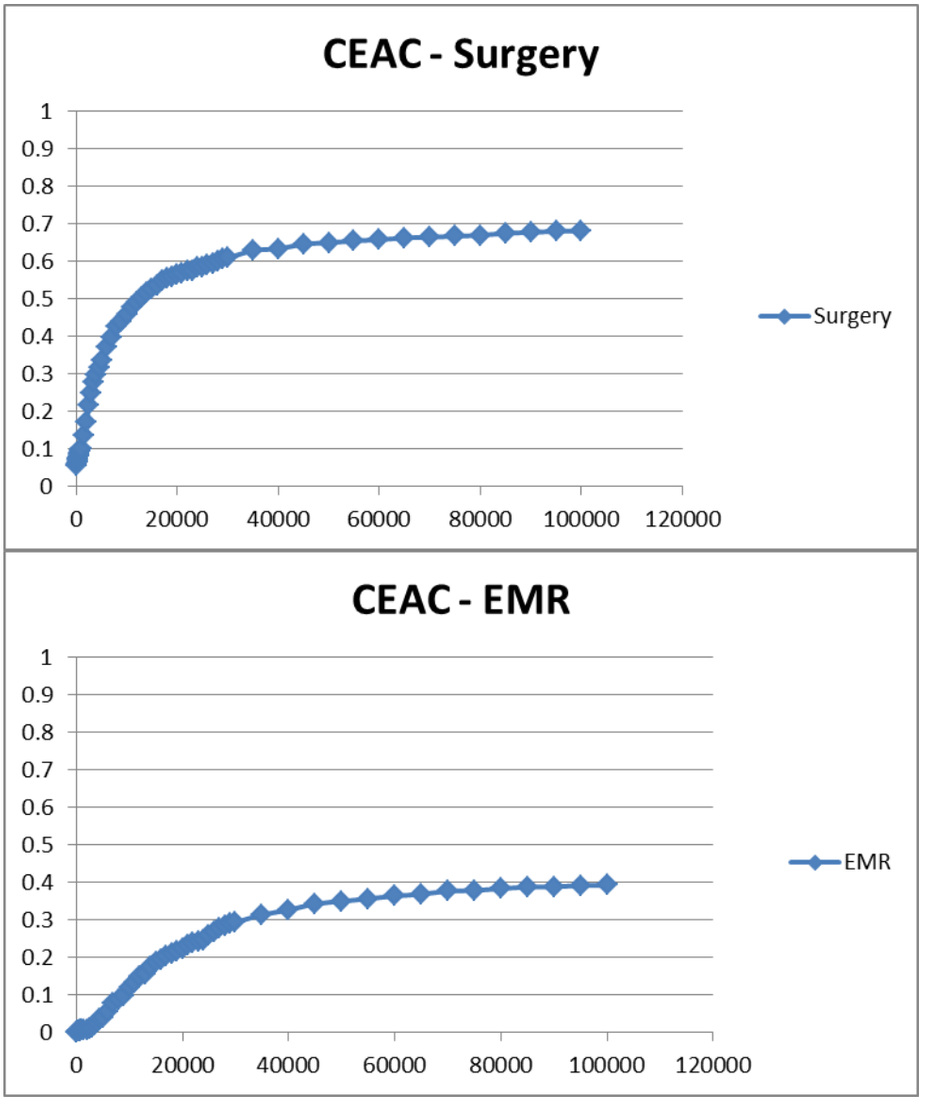
13.11.1 QALY breakdown

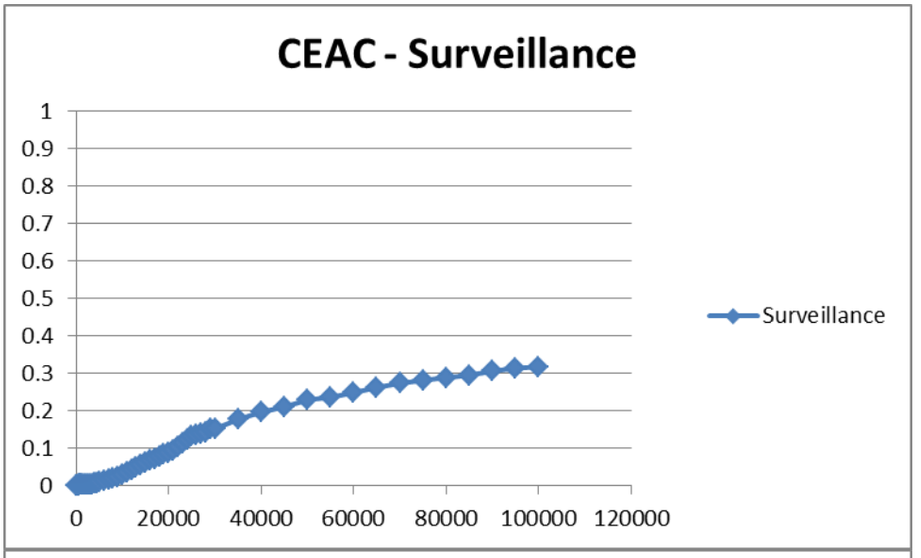


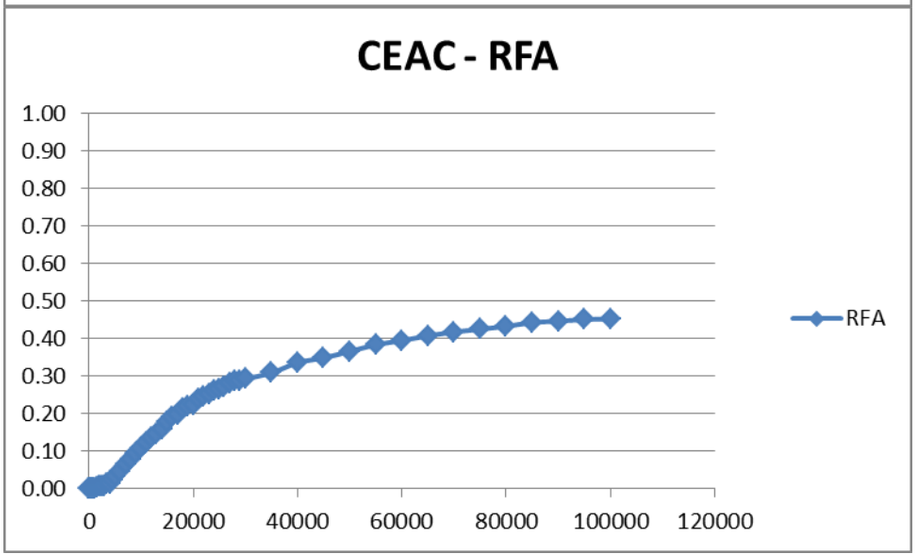
13.11.2 Cost breakdown



13.12 Cost effectiveness acceptability curves




CEAC - Surveillance
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20000
40000
60000
80000
100000
120000
Surveillance


CEAC - RFA
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
20000
40000
60000
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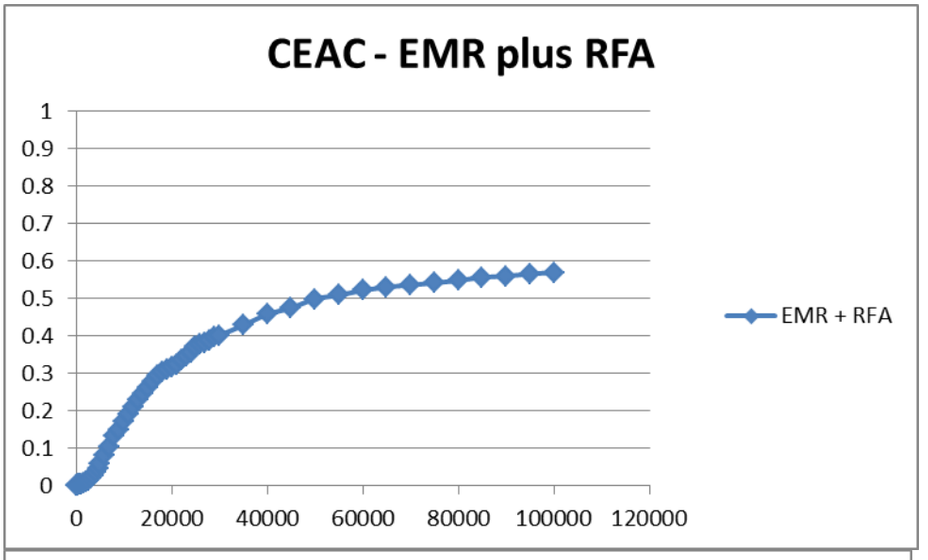
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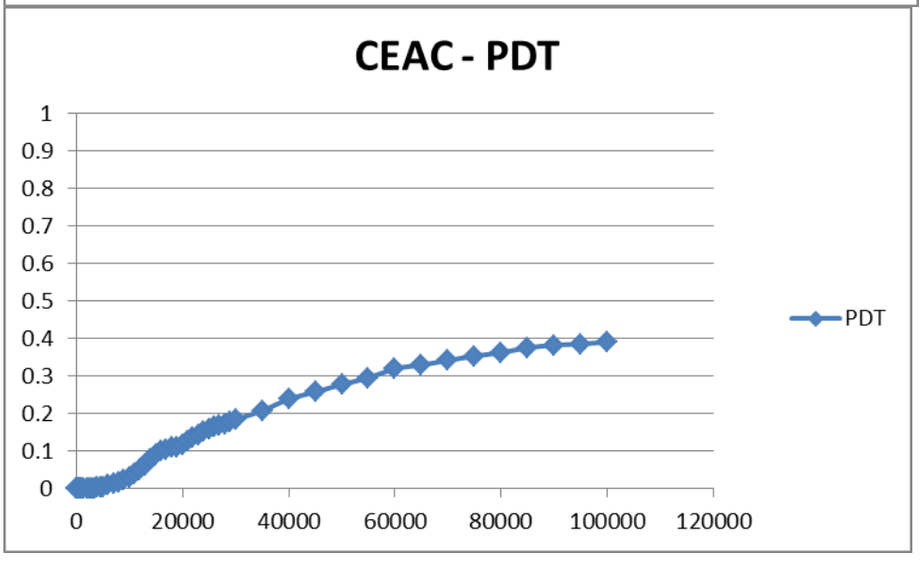
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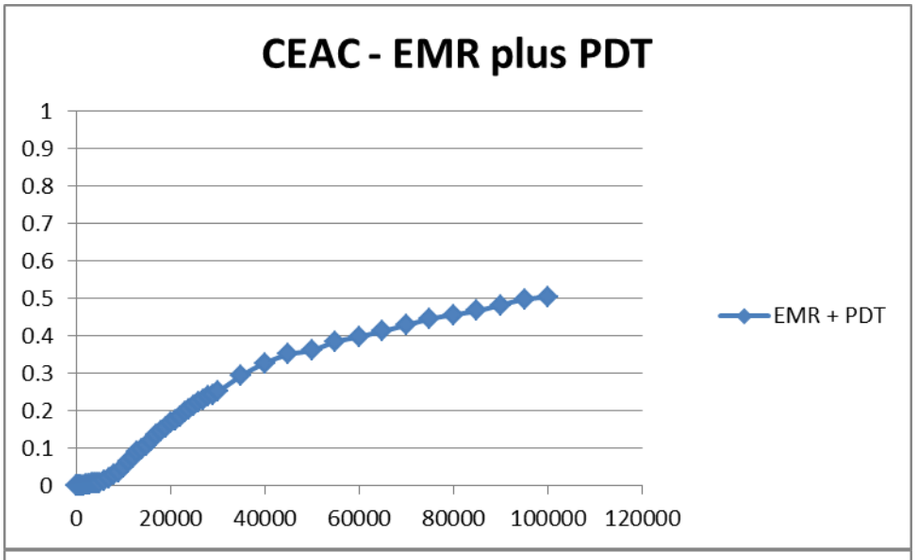
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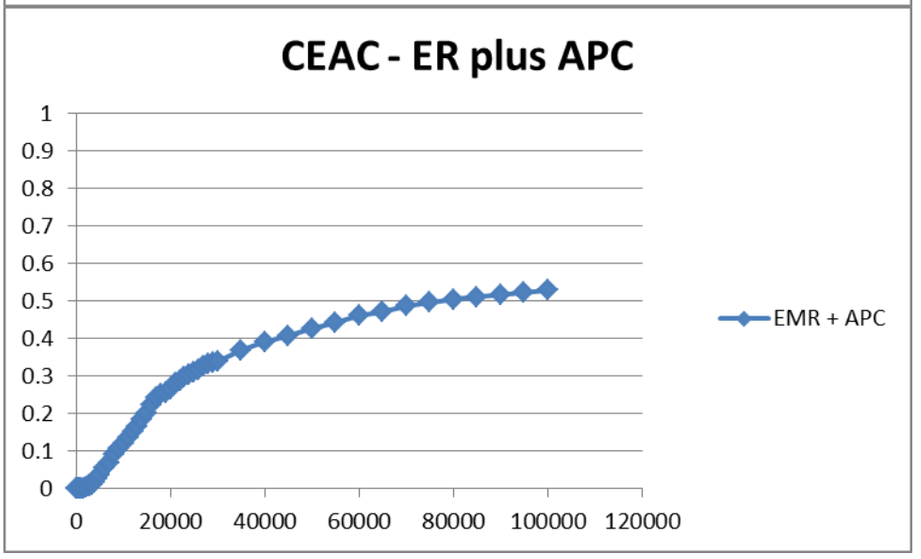
CEAC - ER plus APC
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13.13 Quality checklist for de novo cost effectiveness

Barrett's oesophagus cost effectiveness modeling P Kandaswamy 2010		
Guideline topic: Barrett's oesophagus	Question no:	
Check list completed by Prashanth Kandaswamy		
Section 1: Applicability	**Yes/ Partly/ No/ Unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the guideline?	Yes	HGD 50 year old
1.2 Are the interventions appropriate for the guideline?	Yes	All appropriate interventions included
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5 Are all direct health effects on individuals included?	Yes	No quality of life included
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Yes	
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	Had to use VAS/TTO and combine with EQ-5D
1.10 Overall judgement: Directly applicable/Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Applicable		
Other comments		

Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline*	**Yes/Partly/No/ Unclear/NA Comments**	**Comments**
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in	Yes	

costs and outcomes?		
2.3 Are all important and relevant health outcomes included?	Yes	
2.4 Are the estimates of baseline health outcomes from the best available source?	Yes	
2.5 Are the estimates of relative treatment effects from the best available source?	Yes	Best quality studies identified from clinical review
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	NHS specific
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Is there no potential conflict of interest?	Yes	
2.12 **Overall assessment**: Minor limitations/Potentially serious limitations/Very serious limitations Minor Limitations		